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(54) Title: SLOW RELEASE PHARMACEUTICAL PREPARATION AND METHOD OF ADMINISTERING SAME

(57) Abstract: A pharmaceutical preparation adopted for sustained release of an active agent(s) over an extended period of time at a therapeutic rate without an initial burst release of the agent(s) upon administration, wherein the preparation comprises: (i) an outer portion prepared from one or more layers of a biodegradable polymer, which is selected to release an active agent over an extended period of time when positioned *in situ* in a patient, and (ii) an inner portion comprising a plurality of micro-capsules formed from at least a biodegradable polymer, said micro capsules containing at least an active agent, wherein the micro-capsules are compressed into the form of a tablet under suitable pressure to suppress the rate of release of the active agent from the micro-capsules. The present specification also relates to a method for inserting one or more implants(s) into a tissue of a mammal comprising the following steps: a) making a small incision into the tissue with a needle and a first sheath; b) withdrawing the needle from the first sheath but leaving the first sheath in the tissue; c) dilating the opening of the incision by inserting a dilator and second sheath of larger diameter through the body of the first sheath; d) withdrawing the dilator from the second sheath, but leaving the second sheath in the tissue; e) disturbing the implant(s) from a sheath filled with implant(s) by inserting said sheath into the final sheath inserted into the tissue and pushing a dilator into the sheath thereby releasing said implant(s) into the tissue.

WO 02/17971 A1

Slow Release Pharmaceutical Preparation and Method of Administering of Same

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical preparation capable of releasing an active agent or agents at a suitable therapeutic rate for a period of time without an initial burst release of active agent upon administration. In particular, the invention provides an improved implant for the sustained administration of a biologically active compound suitable for subcutaneous implantation. The invention also relates to methods for making, using and administering the preparation and the implant of the invention as well as a method of treating a patient using the preparation.

BACKGROUND ART

The benefits of sustained release pharmaceutical preparations are well known in the art. Many therapeutic agents have a short half-life and or are rapidly cleared (metabolised) from mammalian bodies requiring frequent or repeated administration of the therapeutic agent to bring about a therapeutic effect in a patient.

A wide variety of different sustained release pharmaceutical preparations are known in the art. Some sustained release pharmaceutical preparations are "matrix" type, and comprise an active compound dispersed in a matrix of a carrier material. The carrier material may be porous or non-porous, solid or semi-solid, and permeable or impermeable to the active compound. Matrix devices may be biodegradable, i.e., they may slowly erode after administration. Alternatively, matrix devices may be nondegradable, and rely on diffusion of the active compound through the walls or pores of the matrix. Matrix devices may be easily prepared, but are not suitable for all compounds. Furthermore, it is difficult to prepare matrix devices that release active compound at a constant rate (i.e., zero order kinetics). Generally, the release rate is typically a function of the active compound's concentration in the matrix.

There are however, many problems with existing implants when used to administer therapeutic agents to patients. First, they deliver a high dose of active agent within a first few days of implantation before reaching a plateau rate of delivery for the majority of the lifespan of the implant. This is due to an initially high rate of absorption caused by the breakdown of the surface of the implant.

Second, irritation of tissues surrounding the implant site occurs because of the initial high rate of absorption of the active agent. This results in redness and soreness of the skin immediately around the implant.

Third, there is the problem that a constant rate of release of active agent over a long period of time is difficult to achieve. Generally, the release rate is typically a function of the concentration of the active agent.

A final problem is that existing implants have a relatively short lifespan.

Thus, there is a need for an improved implant, which deliver active agent at a therapeutic rate without an initial rise in concentration of the active agent for an extended period of time.

Throughout the specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

DISCLOSURE OF THE INVENTION

According to the present invention there is provided a pharmaceutical preparation adapted for sustained release of an active agent(s) over an extended period of time at a therapeutic rate without a significant burst release of the agent(s) upon administration, wherein the preparation comprises: (i) an outer portion prepared from one or more layers of a biodegradable polymer, which is selected to release an active agent over an extended period of time when positioned *in situ* in a patient, and (ii) an inner portion comprising a plurality of microcapsules formed from at least a biodegradable polymer, said microcapsules containing at least an active agent, wherein the microcapsules are compressed

into the form of a tablet under suitable pressure to constrain the rate of release of the active agent from the microcapsules.

The rate at which an active agent is delivered to a patient may range depending on the therapeutic effect sought. According to the invention, pharmaceutical levels of an active agent in the patient rise to a desired therapeutic level where they will approximately remain over the life of the pharmaceutical preparation. To this extent, preparations of the present invention do not exhibit any significant burst effect of the drug when initially administered to the patient. A burst effect is commonly exemplified by a significant delivery rate rise in the pharmaceutical upon administration to the patient followed by a progressive decline in the delivery rate of the pharmaceutical.

The therapeutic level of the drug that is reached in the serum of the patient should be sufficient for treatment of a patient over an extended period of time and should not cause any ill effects to the patient. Preferably, the release rate is either relatively constant or declines slowly over the *in situ* life span of the tablet or it reduces as the preparation gradually degrades *in situ*. Most preferably, the release rate of the preparation decreases at a rate proportional to the length of time in which the preparation is in the patient. The preparation should, however, be prepared to ensure that the release rate of the active agent is such that an extended therapeutic effect is observed over the expected *in situ* life of the preparation in the patient.

In the process of preparing a pharmaceutical preparation in accordance with the invention particular attention must be had to the pressure used to prepare the inner tablet. The amount of pressure applied in the compression process is proportional to the lifespan of the implant and is inversely proportional to delivery rate. To produce a long lasting pharmaceutical preparation it is desirable to use a high pressure when forming a tablet from the active agent/polymer microcapsule mix. High pressures are used to weld the microcapsules together when forming the implant and thus increasing the strength of the tablet matrix and therefore increasing the durability of the implant. The compaction of the mixture into granulates may be by conventional dry compaction means, for

example pressing, rolling, slugging extrusion etc. Preferably, a sufficiently high pressure should be used such that a force of at least 5 kg is required to fracture the surface of the implanted tablet. Still more preferable are pressures, which will require 6, 7, 8, 9, and 10 kg to fracture the surface of an implanted tablet. Another example of a preferable pressure is, the pressure reading of at least 50 on a Manesty tablet punching machine, model F3.

The size of the microcapsules used in the pellet also has an impact on the lifespan of the implant in a patient. The bigger the microcapsules the greater reduction in absorption of the active agent. Preferably, the size of the microcapsules is greater than 12 microns. In a preferred embodiment, where the active agent is naltrexone the size of a microcapsules is preferably between 30 to 100 microns.

The diameter of the pharmaceutical preparation can range from 3mm to 12 mm Preferably, the diameter is 5mm to 8mm. More preferable is a diameter of 8mm. The height of the pharmaceutical preparation can range from 3mm to 15mm. Preferably the height is 5mm.

By encapsulating an active agent with one or more coatings of a biodegradable polymer to form microcapsules and by compressing those capsules into a tablet, the absorption rate of the active ingredient can be rapidly reduced, thus increasing the period of time that the active agent can act in the body. In particular, the inventors have found that a pharmaceutical preparation possessing the above characteristics has the effect of:

a) removing the initial rise in concentration of active ingredient when the pharmaceutical composition is first implanted;

b) producing a relatively constant delivery rate for the lifespan of the implant;

c) eliminating irritation of the surrounding tissue area caused by the initial rise in concentration of the active ingredient when the pharmaceutical composition is first implanted; and

d) increasing the duration of action of the implant.

To ensure clarity of the description that follows, the following definitions are provided.

The term "active agent" refers to a compound useful for effecting some beneficial change in the subject to which it is administered. For example, "active agents" within the scope of this definition include gastrointestinal therapeutic agents such as aluminium hydroxide, calcium carbonate, magnesium carbonate, sodium carbonate and the like; non-steroidal antifertility agents; parasympathomimetic agents; psychotherapeutic agents; major tranquilizers such as chlorpromazine HCl, clozapine, mesoridazine, metiapine, reserpine, thioridazine and the like; minor tranquilizers such as chlordiazepoxide, diazepam, meprobamate, temazepam and the like; rhinological decongestants; sedative-hypnotics such as codeine, phenobarbital, sodium pentobarbital, sodium secobarbital and the like; steroids such as testosterone and testosterone propionate; sulfonamides; sympathomimetic agents; vaccines; vitamins and nutrients such as the essential amino acids; essential fats and the like; antimalarials such as 4-aminoquinolines, 8-aminoquinolines, pyrimethamine and the like, anti-migraine agents such as mazindol, phentermine and the like; anti-Parkinson agents such as L-dopa; antispasmodics such as atropine, methscopolamine bromide and the like; antispasmodics and anticholinergic agents such as bile therapy, digestants, enzymes and the like; antitussives such as dextromethorphan, noscapine and the like; bronchodilators; cardiovascular agents such as anti-hypertensive compounds, Rauwolfia alkaloids, coronary vasodilators, nitroglycerin, organic nitrates, pentaerythritotetranitrate and the like; electrolyte replacements such as potassium chloride; ergotalkaloids such as ergotamine with and without caffeine, hydrogenated ergot alkaloids, dihydroergocristine methanesulfate, dihydroergocornine methanesulfonate, dihydroergokroyptine methanesulfate and combinations thereof; alkaloids such as atropine sulfite, Belladonna, hyoscine hydrobromide and the like; analgetics; narcotics such as codeine, dihydrocodienone, hydromorphine, meperidine, morphine and the like; narcotic antagonists such as naltrexone and naloxone and the like; non-narcotics such as salicylates, aspirin, acetaminophen, d-propoxyphene and the like; antibiotics such as the cephalosporins, chloranphenical, gentamicin, Kanamycin A, Kanamycin B, the penicillins, ampicillin, streptomycin A, antimycin A,

chloropamtheniol, metromidazole, oxytetracycline penicillin G, the tetacyclines, and the like; anti-cancer agents; anti-convulsants such as mephenytoin, phenobarbital, trimethadione; anti-emetics such as thiethylperazine; antihistamines such as chlorophinazine, dimenhydrinate, diphenhydramine, perphenazine, tripelennamine and the like; anti-inflammatory agents such as hormonal agents, hydrocortisone, prednisolone, prednisone, non-hormonal agents, allopurinol, aspirin, indomethacin, phenylbutazone and the like; prostaglandins; cytotoxic drugs such as thiotepa, chlorambucil, cyclophosphamide, melphalan, nitrogen mustard, methotrexate and the like; antigens of such microorganisms as Neisseria gonorrhea, Mycobacterium tuberculosis, Herpes virus (humonis, types 1 and 2), Candida albicans, Candida tropicalis, Trichomonas vaginalis, Haemophilus vaginalis, Group B Streptococcus ecoli, Microplasma hominis, Hemophilus ducreyi, Granuloma inguinale, Lymphopathia venereum, Treponema pallidum, Brucella abortus, Brucella melitensis, Brucella suis, Brucella canis, Campylobacter fetus, Campylobacter fetus intestinalis, Leptospira pomona, Listeria monocytogenes, Brucella ovis, Equine herpes virus 1, Equine arteritis virus, IBR-IBP virus, BVD-MB virus, Chlamydia psittaci, Trichomonas foetus, Toxoplasma gondii, Escherichia coli, Actinobacillus equuli, Salmonella abortus ovis, Salmonella abortus equi, Pseudomonas aeruginosa, Corynebacterium equi, Corynebacterium pyogenes, Actinobaccilus seminis, Mycoplasma bovigenitalium, Aspergillus fumigatus, Absidia ramosa, Trypanosoma equiperdum, Babesia caballi, Clostridium tetani, and the like; antibodies that counteract the above microorganisms; and enzymes such as ribonuclease, neuramidinase, trypsin, glycogen phosphorylase, sperm lactic dehydrogenase, sperm hyaluronidase, adenosinetriphosphatase, alkaline phosphatase, alkaline phosphatase esterase, amino peptidase, trypsin, chymotrypsin, amylase, muramidase, acrosomal proteinase, diesterase, glutamic acid dehydrogenase, succinic acid dehydrogenase, beta-glycophosphatase, lipase, ATP-ase alpha-peptate gamma-glutamylotranspeptidase, sterol-3-beta-ol-dehydrogenase, and DPN-di-aprorase. Other suitable active agents include testosterone, progesterone and estrogens such as diethyl stilbestrol, 17-beta-estradiol, estrone, ethinyl estradiol, mestranol, and the like; progestins such as norethindrone, norgestryl, ethynodiol diacetate, lynestrenol,

medroxyprogesterone acetate, dimesthisterone, megestrol acetate, chlormadinone acetate, norgestimate, norethisterone, ethisterone, melengestrol, norethynodrel and the like; and spermicidal compounds such as nonylphenoxypolyoxyethylene glycol, benzethonium chloride, chlorindanol and the like. In one preferred embodiment, the active agent is naltrexone.

The term "effective amount" as applied to "one or more active agents" refers to that amount which is sufficient to effect the desired change in the subject. It is within the knowledge and skill of a person skilled in the art to determine the effective amount of an active agent.

By "microcapsules" is meant particles that contain an active agent dispersed or dissolved within a biodegradable, biocompatible polymer that serves as the matrix of the particle.

By "biodegradable" is meant a material that should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. The products of the biodegration should also be biocompatible with the body.

By "biocompatible" is meant not toxic to the human body, is pharmaceutically acceptable, is not carcinogenic, and does not significantly induce inflammation in body tissues.

The term "treatment" as used herein covers any treatment of a disease in an animal (including a human), and includes: (i) preventing the disease from occurring; (ii) inhibiting the disease, i.e., arresting its development; (iii) relieving the disease, i.e., causing regression of the disease; or (iv) modifying normal biological activity such as in the case of promotion of weight gain or contraception.

While the pharmaceutical preparations prepared herein may be administered in any form, preferably they are delivered as implants adapted for drug delivery beneath subcutaneous tissue.

The term 'implant(s)' refers to any object that may be required to be administered to a patient for a pharmaceutical effect including the pharmaceutical preparation of the present invention. For the purposes of this specification, the term 'implant(s)' refers to a pharmaceutical preparation comprising an active agent. In a preferred embodiment, the implant comprises at least naltrexone or like substance as the active agent.

The preparation of the invention can be administered to any mammal. Preferably, the mammal is a human being.

The effective amount of active agent can be determined by a person skilled in the art. When the active agent is naltrexone, the effective amount of naltrexone is about 1g to about 20g. Preferably, the effective amount is about 3g to about 15g. Still more preferable is a dosage range of about 3.6g to about 7.2g.

The implants of the present invention are adapted to deliver active agent at a constant rate for an extended period of time. Where the active agent is, for example, naltrexone the rate of delivery is preferably about 0.1mg per day to 30 mg per day. More preferably the rate of delivery is 0.5mg per day to 30 mg per day with delivery rates between 1mg per day to 5 mg per day being even more desirable. Still more desirable are delivery rates between 3 mg per day to 10 mg per day. Most desirable are delivery rates of 3.6 mg per day to 14.4 mg per day.

Another way to express delivery rates is by multiplying the percentage of active agent delivered per day by the amount of active agent remaining in the implant. The percentage of active agent delivered per day can range from 1% per day to 10% per day. Preferably the percentage per day is 0.2% per day, 0.4% per day or 0.8% per day.

Preferably, the length of time which the implants can deliver active agent is for more than 40 days. More preferable is a duration of delivery of over 45 days. More preferable is a duration of delivery of over 50 days. More preferable is a duration of delivery of over 3 months. Still more preferably the duration of delivery is over 6 months. Even more preferably the duration of delivery is over 1 year. Still more desirable the duration of delivery is over 2 years. A preferred

embodiment is a pharmaceutical composition comprising naltrexone having a lifespan of more than 40 days, more preferably more than 45 days, more preferably more than 50 days, more preferably more than 3 months, more preferably over 6 months and still more preferably over 1 year and even more desirably over 2 years. Still more desirable is a lifespan of at least 3 years.

One factor which contributes to the ability to achieve the duration periods described in the above paragraph is that the biodegradable polymer softens during a period which results in an increase in the release rate of active agent. The release rate is increased to a rate which is about the same as when the implant was first administered. Such an increase in release rate, increases the lifespan of the implant, provided that the rate of degradation of the biodegradable polymer is similar to the rate of release of active agent.

The polymeric matrix material of the microcapsules of the present invention is a biocompatible and biodegradable polymeric material. Preferably, the biodegradable polymer used in the preparation of the pharmaceutical preparation is long lasting. The matrix material should be biodegradable in the sense that the polymeric material should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. Preferably, the length of time that the biodegradable polymer stays intact is more than 40 days, more preferably the biodegradable polymer stays intact for a length of time of over 45 days. More preferably the biodegradable polymer stays intact for a length time of over 50 days. More preferably the biodegradable polymer stays intact for a length of time of over 3 months, still more preferably, more than 6 months and still more preferably more than 1 year. The coating should however allow the active agent to diffuse out of the implant and into the surrounding blood stream and its thickness can be altered to control this role. Therefore when the coating is present, the implant is still able to release active agent. Suitable examples of polymeric matrix materials include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxaates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein,

and waxes, such as, glycerol mono-and distearate, and the like. Purasorb-Poly DL-Lactide with an inherent viscosity in the range of 0.1dl/g to 1.8 dl/g is preferable. The most preferred polymer for use in the practice of this invention is Purasorb-Poly DL-Lactide with a molecular weight of 24 800 and inherent viscosity of 0.50 dl/g. An example of another biodegradable polymer is Poly DL-Lactide/glycolide copolymer with inherent viscosity of 0.90 dl/g.

The inventors have also found that coating the compressed tablets formed from a plurality of microcapsules with one or more layers of a biodegradable polymer reduces the absorption rate of the active ingredient. Another effect of using a coating around the tablets is to reduce the risk of tissue irritation caused by direct contact of the active agent with surrounding tissue. Preferably, a tablet is coated with at least one layer of biodegradable polymer. It is more preferable if a tablet is coated with at least 2 layers of biodegradable polymer. It is even more preferable if a tablet is coated with at least 3 layers or more of biodegradable polymer.

A plurality of tablets can be coated with a biodegradable polymer to further reduce the absorption rate of the active agent. Thus two or more tablets can be formed into one pellet by coating the tablets with a biodegradable polymer. The rate of absorption of such a pellet is lower than that of an equivalent sized implant made from one tablet. This may be due to the number of coatings of biodegradable polymer and reduced surface area of active agent exposed. Preferably there is one coating of biodegradable polymer. More preferably, there are two coatings of biodegradable polymer. Still more preferably, there are three coatings of biodegradable polymer. Where a plurality of tablets are formed together as a single implant different tablets may have different release rates. For example, 0.4 % and 0.2% tablets may be formed together in a single implant.

The pellets described above can contain one or more tablets comprising different active agents, each active agent having different rates of release. For example one tablet may comprise of oestrogen, a second tablet may comprise progesterone and a third tablet may comprise testosterone.

The thickness of the coating of biodegradable polymer surrounding the tablet may affect the absorption rate of the active ingredient. The greater the thickness of the coating, the greater the reduction in absorption rate of the active agent. Preferably the thickness of the coating is 0.001mm to 1mm. More preferably the thickness is 0.01mm to 0.1mm. Still more preferably the thickness is 0.1mm to 1mm. An example of a suitable thickness of the coating is 0.6mm.

The microcapsule product used in the present invention can be prepared by any method capable of producing microcapsules in a size range acceptable for use in the compressed tablets. In these methods, the material to be encapsulated (ie the active agents) is generally dissolved, dispersed, or emulsified, using known mixing techniques, in a solvent containing the wall-forming material. Solvent is then removed from the microcapsules and thereafter the microcapsule product is obtained. An example of a conventional microencapsulation process is disclosed in U.S. Pat. No. 3,737,337 wherein a solution of a wall or shell forming polymeric material in a solvent is prepared. The solvent is only partially miscible in water. A solid or core material is dissolved or dispersed in the polymer-containing solution and, thereafter, the core-material-containing solution is dispersed in an aqueous liquid that is immiscible in the organic solvent in order to remove solvent from the microcapsules. Another example of a process in which solvent is removed from microcapsules containing a substance is disclosed in U.S. Pat. No. 3,523,906. In this process, a material to be encapsulated is emulsified in a solution of a polymeric material in a solvent that is immiscible in water and then the emulsion is emulsified in an aqueous solution containing a hydrophilic colloid. Solvent removal from the microcapsules is then accomplished by evaporation and the product is obtained.

The microcapsules can be mixed by size or by type so as to provide for the delivery of active agent to the patient in a multiphasic manner and/or in a manner that provides different agents to the patient at different times, or a mixture of agents at the same time.

Pharmaceutical excipient can also be used in the implants of the invention. Suitable excipient are well known in the art and include starch, cellulose, talc,

glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride and dried skim milk.

While pharmaceutical excipients may be incorporated in the inventive pharmaceutical preparation it should be observed that it is not desirable to incorporate significant amounts of disintegration agents that might have the effect of increasing the rate of degradation of the tablet. Such agents are preferably not included in the tablet formulation.

Pharmaceutical preparations prepared according to the invention will have broad application in treating patients in need of long term treatment of the active agents described herein. According to one embodiment the present invention provides a method of treating a patient by administering a pharmaceutical preparation as described herein to said patient.

According to one embodiment the invention provides a method of treating a patient comprising the steps of:

(1) administering implant(s) of the invention comprising about 3.6g of naltrexone where 0.4% per day of the naltrexone mass is released;

(2) after about 3 to 6 months repeating step 1; and

(3) after about a further 6 months administering implant(s) of the present invention comprising about 3.6g to 7.2g of naltrexone where 0.2% per day of the naltrexone mass is released.

According to another embodiment the invention provides a method of treating a patient comprising the steps of:

(1) administering implant(s) of the present invention comprising about 1.8g of naltrexone releasing at 0.2% per day and a second 1.8g of naltrexone releasing at 0.4% per day;

(2) after about 90 days administering implant(s) of the present invention comprising about 3.6g of naltrexone releasing at 0.2% per day; and

(3) if necessary, repeating step (2) after a period of 6 to 18 months.

According to a third embodiment there is provided a method of treating a patient who requires a greater rate of delivery per day than provided in the above embodiments. Such patients include those who are of large mass. This embodiment comprises the steps of:

(1) administering implant(s) of the present invention comprising about 1.8g to 3.6g where the percentage delivered per day is 0.4% and 0.2% respectively; and

(2) after about 12 months administering implant(s) of the present invention comprising 5.4g naltrexone where 0.2% per day of the naltrexone mass is released.

It should be appreciated that the pharmaceutical preparation of this invention may be administered to a patient in any suitable manner for which the active agent(s) is designed to be administered. Most preferably, the preparation(s) are designed for subcutaneous administration, preferably in the subcutaneous tissue of the abdominal wall. In the alternative however, the preparations may be subcutaneously administered to other body cavities for example, vaginally, nasally and sublingually.

Accordingly one method for inserting one or more pharmaceutical preparations into a tissue of a mammal comprises the following steps:

a) making a single small incision into the tissue with a needle and first sheath;

b) withdrawing the needle from the first sheath, but leaving the first sheath in the tissue;

c) dilating the opening of the incision by inserting a dilator and second sheath of larger diameter through the bore of the first sheath;

d) withdrawing the dilator from the second sheath; and

e) dispensing the preparation by inserting it through the second sheath in the tissue.

If necessary, further dilation of the opening of the initial incision may be achieved by repeating the process of inserting dilators and sheaths of increasing diameter

through the bore of sheaths of smaller diameter, until the diameter of the opening of the incision is sufficiently large to receive the preparation.

The abovementioned method will now be described in more detail, which should be understood as being preferably to the application of the method. Prior to making the incision with the needle an appropriate dose of local anaesthetic is administered to the site where the incision is to be made.

The diameter of the needle required for the initial incision is preferably less than 5mm and desirably between 1 and 3mm. In one example of the invention the diameter is 2mm.

After the initial incision is made, the needle and sheath are inserted into the subcutaneous tissue of the patient. In this respect the needle desirably resides within the sheath and the two are inserted into the patient as a single unit. To aid penetration of the subcutaneous layer of the patient, the needle preferably protrudes from the sheath in such a manner that it may penetrate the epidermis of a patient before the sheath penetrates the epidermis. In an alternate form, the needle and sheath may be formed as a single unit wherein the needle or central body may be withdrawn from the sheath when inserted into a patient. Where the needle and sheath are formed as a single unit, preferably the sheath is adapted to penetrate a patient's tissue.

Following insertion and location of the needle and sheath, the needle is withdrawn from the sheath leaving the sheath in position protruding into the subcutaneous tissue. In order to dilate the opening of the incision, a dilator and sheath of larger diameter are inserted through the bore of the sheath in the subcutaneous tissue, thereby splitting the sheath left inside the subcutaneous tissue. The split sheath and the sheath and dilator of larger diameter remain in the subcutaneous tissue.

Further dilation of the opening of the incision may be required, depending on the size of the implant(s), which are to be administered. The opening of the incision is further dilated by inserting dilators and sheaths of increasing diameter into the bore of a sheath of smaller diameter, which remains in the subcutaneous tissue.

Dilation is required until such time as the opening of the incision is of a sufficient size to receive the implant(s).

Once the opening of the incision is of a sufficient size to receive the implant(s), the last dilator is withdrawn, but the accompanying sheath is left in the subcutaneous tissue site. A sheath of smaller diameter containing the implant(s) is pushed through the bore of the sheath, which has been left in the subcutaneous tissue. The dilator accompanying the sheath containing the implant(s) is then used to push the implant(s) through the sheath into the subcutaneous tissue.

According to the above method a plurality of implant(s) associated with each dose of active agent are capable of being delivered to a range of areas in the subcutaneous tissue of a patient along one incision track. While any number of implants may be delivered by this means, preferably at least 1 to 20 and more preferably 2 to 15 implants are delivered in a single track. Where multiple implants are delivered the implants are preferably spaced apart. For example, with the one incision, a 1 gram pellet can be spread into the areas at or near the incision, another gram may be delivered further up along the incision track and so on until the requisite number of grams of drug are delivered. Because the subcutaneous fat behaves like fluid, the implant(s) are not restricted to staying along the incision track. The implant(s) can be manipulated from the surface by a finger to spread them around. This reduces the discomfort to the patient of a single large implant. Furthermore, a large dose of drug can be administered from the one incision.

The method for insertion described above has the potential to alleviate the problems associated with delivery of medium and large implant(s). Using this methodology it is possible to deliver one or more implant per incision, thus being able to deliver a large dose of active agent in smaller sized pellets, the patient thus not feeling the discomfort of being inserted with one large pellet. Where more than one implant is delivered to the patient according to the above method, preferably the implants are inserted into the second sheath and forced through it with the aid of the dilator or a like device facilitating extrusion of the implant from

the sheath. Where multiple implants are delivered to a patient the sheath may be withdrawn from the initial incision as the implants are released or all the implants may be extruded from the sheath before it is extracted.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing release rate of prior art implants compared to the release rate of implants of the present invention.

Figure 2 is a graph showing the release rate of encapsulated microcapsules of naltrexone with Poly-DL-lactide *in vitro*.

Figure 3 is a graph showing the effects of pressure and polymer coating on the release rates.

Figure 4 is a custom design implant to release specific drugs at appropriate rates.

Figure 5 is a graph showing naltrexone levels in the blood plasma of rats. The results obtained suggested the amount of drug released *in vivo* on a daily basis. After implantation of the tablets and microcapsules, plasma naltrexone level increased to a peak of 9.2 ng/ml and 14.2 ng/ml, respectively. Possibly, there was an initial burst release of naltrexone from the microcapsules between day 1 and 7. The relatively constant plasma level of naltrexone suggested a relative constant release rate of naltrexone from the tablets. In contrast, the naltrexone microcapsules showed rapid drug release in two weeks after administration. This difference in drug release rates may be due to the larger surface area per unit volume, and the smaller diameter.

Figure 6 shows release rates of naltrexone implants in a water bath expected to release 0.2% naltrexone per day. This graph shows 94% of naltrexone was released at about day 410 and the overall daily release is fairly consistent.

Figure 7 shows release rates of naltrexone implants in a water bath expected to release 0.2% naltrexone per day. This graph shows 53% of the naltrexone was released at the 357 day mark and the overall release rate is fairly consistent.

Figures 8 to 12 shows release rates of naltrexone implants in a water bath expected to release 0.4% naltrexone per day. The graphs show that the release rate is consistent for at least the first 120 days and at about 120 days the implants have released about 35-40% of the naltrexone.

Figure 13 shows release rates of naltrexone implants in a water bath expected to release 0.4% naltrexone per day. The graph shows that the implant releases naltrexone past 200 days and has at about 200 days only released 40-48% of the total mass of the implant.

Figure 14 shows free naltrexone blood serum levels of a patient administered with two implants, each containing 1.8g of naltrexone expected to release 0.2% per day.

Figure 15 shows free blood serum levels of a patient administered with two implants, each containing 1.8g of naltrexone expected to release 0.4% per day.

Figure 16 shows free blood serum levels of approximately 11 patients each administered with 2 implants each containing 1.8g naltrexone releasing at 0.4% per day.

Figure 17 shows free naltrexone blood levels of approximately 5 patients, each administered with 2 implants, each containing 1.8g naltrexone expected to release 0.8% per day. This graph shows that the rate of naltrexone released is still steady at the 200 day mark.

Figure 18 and 18a shows the insertion of a needle and sheath into subcutaneous tissue.

Figure 18b shows the withdrawal of the needle from the sheath.

Figures 18c to 18h show dilation of the opening of the incision with a number of dilators and sheaths.

Figure 19 shows the delivery of a plurality of implant(s) by insertion of at least dilator into a sheath containing one or more implant

Figure 20 shows a sheath containing implant(s).

BEST MODE(S) FOR CARRYING OUT THE INVENTION

Further features of the present invention are more fully described in the following Examples. It is to be understood that the present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Example 1

Implantable Naltrexone.

Previously, patients have put up with an initial bolus dose when an implant is first inserted – commonly known as the "Burst Effect" (see figure 1).

Clinical work shows that for a Naltrexone implant to be effective, the implant should deliver an equivalent dose of 6-800 μg of Naloxone / hour. As Naltrexone is thought to be twice as effective as Naloxone as well as lasting 8 times as long in the body (ie $t_{1/2}$ Naloxone = ½ hour, $t_{1/2}$ Naltrexone = 4 hours), a dose greater than 40 μg/hr of Naltrexone might be potentially effective, as 40 μg /hr is close to being 1 mg/day. Therefore a 1 g Naltrexone implant releasing 0.1% per day should partially block receptors for a period of 1-2 years. Further, 7.2g of naltrexone releasing at 0.2% per day should block receptors for 2 years.

The present invention allows naltrexone to be delivered in a reliable fashion for periods greater than 6 weeks. The herein described pharmaceutical preparation achieves a delivery of 0.5 to 10 mg /day and a corresponding blood level of 0.5 to 3 ng / ml and this is expected to be sufficient to block 15 to 300mg of Morphine delivered intravenously. Furthermore, preparations prepared according to the invention can maintain sufficient blood levels for at least 3 months, preferably at least 3 years.

To achieve a reliable release rate for 3 months, a 1g implant would need to release 2 to 10 mg of drug per day (ie 100 day lifespan ≅ 3 months). A reliable release rate of 6 months may be achieved by a 3.6g implant releasing at 14.4

mg/day, 2 g implant releasing 10 mg / day or a 1 g implant releasing 2 to 5 mg per day. For a period of 12 months, a 2 g implant releasing at 1 to 6 mg / day will have a lifespan of 300 to 1000 days ie approximately equal to 1 to 3 yrs or two 3.6g implants releasing at 14.4.mg/day administered at 0 and 6 months. A period of 18 months may be achieved with a 2 to 3g implant releasing at 1 to 10 mg /day or two 3.6g implants administered at 0 and 6 months releasing at 14.4mg/day and one 7.2g implant administered at 12 months. A 3g implant releasing at 0.5 to 10 mg per day may last for 2 years or longer. Two 3.6g implants administered at 0 and 6 months releasing at 14.4.mg/day and one 7.2g implant administered at 12 months releasing at 14.4mg/day may last for 2 years or longer.

Experimental results has identified the following as being pertinent to achieve said release rates:

1. Encapsulating Naltrexone with a long lasting polymer (Poly-DL-lactide), to form microcapsules of Naltrexone and polymer produced a release rate profile with an initial peak before stabilising and releasing at a relatively constant rate for greater than 2 months (see figure 2). The ratio of naltrexone to Poly-DL-lactide used was 1:1.

2. Punching a tablet from the encapsulated microcapsules under moderate pressure and coating the entire implant with Poly-DL-lactide eliminated the initial peak in the release rate as well as increasing the lifespan of the implant (see figure 3).

3. Coating the tablet a second time (ie increasing the thickness of the Purasorb Poly-DL-lactide coating) – estimated thickness of 0.5 mm and increasing the pressure used to punch the tablet helped to keep a linear release rate profile as well as further increasing the lifespan of the implant – see figure 3

4. Experiments were conducted on the effects of the surface area of the implant with respect to the volume of the tablet. It was shown that by reducing the ratio of the surface area to the volume of the tablet, an

increase in the lifespan was measured. This is confirmed by experiments which demonstrate that a 5mm diameter implant released Naltrexone at a rate of 0.6% per day in comparison to an 8mm diameter tablet which released Naltrexone at 0.25% per day.

5. Another method of forming the implant was implemented to further increase the lifespan of an implant. Punching 5 tablets of 5 mm diameter and 1 mm high from encapsulated microcapsules of naltrexone and individually coating these implants (ie creating a series of "pancakes"), with Purasor Poly DL and then holding these 1 mm high tablets together and further coating the lot with Poly-DL-lactide to form one implant, the lifespan of the implant was much greater than an equivalent sized implant made from one pellet. This may be due to the coatings and reduced surface area which delayed absorption by 4 times – see Table 1 and Figure 3.

Table 1: Influence of various manufacturing processes on the release rate of naltrexone **(ACTUAL VALUES):**

Days	% Released, medium pressure, no polymer coat	% Released, medium pressure, 1 polymer coat	% Released, high pressure, 2 polymer coats
0	0	0	0
1	26.01	2.69	0.64
2	34.36	4.22	1.43
4	42.52	7.73	*2.54
5	43.92	*9.13	3.1
6	44.75	*10.53	3.7
8	45.98	13.33	*4.73
9	*46.55	14.83	*5.24
10	47.12	*16.34	*5.75
11	47.79	*17.86	*6.27
15	*48.68	*23.92	8.32
17	*49.13	26.95	*9.33
20	49.8	*29.76	*10.84
25	52.32	34.43	*13.36
30	53.79	38.05	15.9
40	-	42.61	21.23

* - Interpolated values

7. In order to eliminate the organic solvent from the tablet that was used in the coating of the tablet, the coated implant was stored under pressure

that was slightly lower than atmosphere pressure and in a hot room overnight to evaporate the solvent from the tablet. The solvent evaporating point was 39 °C and the hot room was maintained at 50 °C thus such conditions would allow any solvent remaining in the tablet to evaporate overnight.

8. Using a single long implant has the disadvantage of causing the patient discomfort pain or possibly breaking the implant if the patient were to bend or move tissue around the implant site. Thus the method of using a series of pellets to achieve the required mass of the implant was developed so that any movement of the surrounding tissue site could be accommodated by the implant without causing any patient discomfort or breakage of the implant. This also allows injections of cassettes of spheres or tablets into an area of subcutaneous tissue.

The use of the described technique on implants was verified by laboratory water bath experiments and human blood serum level experiments. The laboratory water bath experiments demonstrated that implants made from the above techniques were releasing 0.2% per day and 0.4% per day in buffer solution. This predicts a lifespan in the order of 1 – 2 years. The human blood serum level experiments demonstrated that implants made from the above techniques were releasing 0.2%, 0.4% and 0.8% per day. This predicts a lifespan of the order of 1 to 2 years.

Example 2

The following example demonstrates how the invention can be used to develop a custom implant, which can release individual drugs at varying rates according to the design.

Hormone replacement therapy can currently be delivered by means of slow release transdermal patches, oral tablets or implants. Typical hormones used are oestrogen, progesterone and testosterone. The prior art consists of individual implants of said hormones, which typically last for periods of 1 to 4 months.

Transdermal patches such as Estraderm, typically have to be replaced every 4 days. This lifespan is relatively short when compared to the required treatment time. Another problem associated with transdermal patches are problems encountered by varying absorption rates through different types of skin.

Quite often a combination of hormones can be used as opposed to individual hormones. In some instances, a combination of hormones may prove to be a more effective means of hormone replacement therapy.

Orally administered hormone tablets are another version of the prior art. Problems arise from the failure to maintain oral tablets. Reasons for the failure may be attributed to the inconvenience of having to take the tablets daily, forgetting to take the tablets daily or ceasing treatment due to the emotional stigma of having to remain on hormone replacement tablets.

Through methods discussed in this invention, a custom implant may be designed to deliver a combination of the above hormones at rates appropriate to each hormone. Such a varied delivery system may be built into the one implant as illustrated in figure 4.

In order to achieve a variety of release rates from the one implant, the following procedure may be used.

To achieve a release rate of:

- 2% per day of oestrogen
- 1% per day progesterone
- 0.5% per day testosterone

} All from the one implant

Thus according to this example oestrogen was encapsulated in microcapsules prepared from 1 week lifespan PGA polymer. The oestrogen tablets were then punched under maximum pressure. These tablets were then coated with 1 month lifespan PGA polymer.

Further progesterone was encapsulated in microcapsules prepared with 1 month lifespan PGA polymer. The progesterone tablets were then punched under maximum pressure and were coated with 1 month lifespan PGA polymer.

Finally testosterone was encapsulated in microcapsules prepared from 6 month lifespan PGA polymer. Testosterone tablet were then prepared under maximum pressure and coated with 6 month lifespan PGA polymer

All three hormone implants were then stacked together coated with 6 month lifespan PGA polymer. With this formulation, an implant may be generated according to figure 4, with each individual drug releasing at an appropriate rate specific to that drug.

Example 3

Naltrexone delivery rates in Rats

To measure naltrexone plasma levels rats were implanted with naltrexone implants produced according to the present invention. Figure 5 presents data showing naltrexone levels in the blood plasma of rats. The results obtained suggested the amount of drug released *in vivo* on a daily basis. After implantation of the tablets and microcapsules, plasma naltrexone level increased to a peak of 9.2 ng/ml and 14.2 ng/ml, respectively. Possibly, there was an initial burst release of naltrexone from the microcapsules between day 1 and 7. The relatively constant plasma level of naltrexone suggested a relative constant release rate of naltrexone from the tablets. In contrast, the naltrexone microcapsules showed rapid drug release in two weeks after administration. This difference in drug release rates may be due to the larger surface area per unit volume, and the smaller diameter.

Example 4

Water bath experiments with Naltrexone delivery rates

The following water bath research was carried to establish that naltrexone tablets have release rates for the 0.2% / day implants.

8mm Tablets comprising naltrexone as the active ingredients produced according to the present invention were subjected to water bath examination Data from these experiments are presented in Figures 6 and 7. Figure 6 shows 94% of the naltrexone mass released at day 410 and the overall daily release rate is pretty consistent. Figure 7 shows 53% of the naltrexone mass released at

the 357 day mark, the overall release rate is also pretty consistent. Note that during a corresponding period in Figure 6, the total release was around 70%. This difference illustrates differences between manual punching which was used to produce the tablets used in Figure 6 and automatic punching which was used in Figure 7 – the pressure of the punch in Figure 7 is higher and is what we are currently using.

Therefore based on the data in Figure 7 a 0.2% / day implant should continue to release active ingredient till the 500+ day mark. Data in figure 6 shows release of active agent to the 410 day mark.

Figures 8 to 12 shows release rates of naltrexone implants in a water bath expected to release 0.4% naltrexone per day. The graphs show that the release rate is consistent for at least the first 120 days and at about 120 days the implants have released about 35-40% of the naltrexone.

Figure 13 shows release rates of naltrexone implants in a water bath expected to release 0.4% naltrexone per day. The graph shows that the implant releases naltrexone past 200 days and has at about 200 days only released 40-48% of the total mass of the implant.

Example 5

Delivery of Naltrexone

The following example illustrates 3 types of implants. These are implants releasing at 0.2% of its naltrexone mass per day, 0.4% / day and 0.8% / day all produced according to the present invention.

The slower the release rate, the longer the implant will last. Clinically, 0.2% per day implants don't really achieve high enough blood levels in the first 100 days to completely block cravings and heroin use, however after 100 days they start to release enough to block cravings and heroin use. This is best demonstrated by Figure 14 from a patient who was implanted with 2 x 0.2% / day implants.

Blood serum levels from patients implanted with 2 x 0.4% / day implants show good blood serum levels and therefore good coverage up to 130 – 150 days (and

probably more however we only have data up to 166 days). These implants give good coverage in the first 100+ days however you would expect them to run out quicker than the 0.2%/day implants as they have released more initially. This is illustrated by Figures 15 and 16.

Data from the 0.8% / day implants shows that good levels are achieved initially (as expected from the 0.4% data). One would expect the patients with 2 x 0.4% / day implants to also have good levels in excess of the 200+ day mark based on this and water bath data. This is highlighted by Figure 17, which shows data from patients implanted with 2 x 0.8% / day implants with some patients registering good levels at the 200+ day mark.

Example 6

Method of Administration of Implantable Naltrexone

Described below is an example of the present invention, wherein the implant is naltrexone. Preferably the diameter of a naltrexone implant ranges from 5mm to 8mm

In Figure 18 and Figure 18a a needle 1 and sheath 2 are inserted into subcutaneous tissue 3 to make an incision 4 having the width of the needle 1 and sheath 2. Preferably, the diameter of the needle is 2mm. Sheath 2 has a sheath hub 5 at the sheath proximal end and bore 6 adapted to receive needle 1. Figure 18b shows the removal of needle 1 from the sheath 2, whilst keeping the sheath 2 inserted in the incision 4 and subcutaneous tissue. Needle 1 has a needle hub 7 at the needle proximal end.

Dilation of the opening of the incision 4 can be achieved by inserting a dilator 8 and sheath 9 of a diameter larger than that of the needle and sheath 2 into the bore 6 of sheath 2 and through sheath 2 such that sheath 2 is split into two pieces 10 and 11 as shown in Figures 18c, 18d and 18e. The two pieces 10 and 11 of sheath 2, remain in the subcutaneous tissue. Preferably, the diameter of dilator 8 is 4mm. Dilator 8 is then removed from sheath 9, but sheath 9 remains in incision 4 and in the subcutaneous tissue 3.

Further dilation is required. Thus, in Figure 18f, dilator 12 and sheath 13 of larger diameter than dilator 8 and sheath 9 are provided. Preferably, the diameter of dilator 12 is 6mm. Further dilation of the opening of the incision 4 can be achieved by inserting a dilator 12 and sheath 13 of a diameter larger than that of sheath 8 through the bore 14 of sheath 8 such that sheath 8 is split into two pieces 15 and 16 as shown in Figures 18f and 18g. Preferably, the diameter of dilator 12 is 6mm. Dilator 12 is then removed from sheath 13, but sheath 13 remains in the incision 4 and the subcutaneous tissue 3, as shown in Figure 18h.

Figure 19 shows that the opening of the incision is of a sufficient size to receive the implant(s). The last dilator 12 is removed, but the accompanying sheath 13 is left in the site. A sheath 17 of smaller diameter which can accommodate the implant(s) 18 and containing implant(s) is pushed through the bore 19 of sheath 13 which has been left in the site. The dilator 20 accompanying the sheath 17 containing the implant(s) is then used to push the implant(s) 18 through the bore 21 of sheath 17 into the subcutaneous tissue.

Figure 20 shows a sheath containing implant(s).

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively, and any and all combinations or any two or more of the steps or features.

The Claims Defining the Invention are as Follows

1. A pharmaceutical preparation adapted for sustained release of an active agent(s) over an extended period of time at a therapeutic rate without an initial burst release of the agent(s) upon administration, wherein the preparation comprises:
   (i) an outer portion prepared from one or more layers of a biodegradable polymer, which is selected to release an active agent over an extended period of time when positioned *in situ* in a patient, and
   (ii) an inner portion comprising a plurality of micro-capsules formed from at least a biodegradable polymer, said micro capsules containing at least an active agent, wherein the micro-capsules are compressed into the form of a tablet under suitable pressure to suppress the rate of release of the active agent from the micro-capsules.

2. A pharmaceutical preparation according to claim 1 wherein the release rate is relatively constant over the *in situ* lifespan of the tablet.

3. A pharmaceutical preparation according to claim 1 wherein the release rate reduces as the pharmaceutical preparation gradually degrades *in situ*.

4. A pharmaceutical preparation according to claim 3 wherein the release rate of the preparation decreases at a rate proportional to the length of time in which the pharmaceutical preparation is in the patient.

5. A pharmaceutical preparation according to claim 1 wherein the release rate of the preparation increases for a period of time as the biodegradable polymer softens.

6. A pharmaceutical preparation according to any one of the preceding claims wherein the suitable pressure is proportional to the lifespan of the implant and is inversely proportional to delivery rate.

7. A pharmaceutical preparation according to any one of the preceding claims wherein the suitable pressure is high pressure.

8. A pharmaceutical preparation according to claim 7 wherein a sufficiently high pressure should be used such that a force of at least 5 kilograms is required to fracture the surface of the implanted tablet.

9. A pharmaceutical preparation according to claim 8 wherein the force is selected from 6, 7, 8, 9 and 10 kilograms.

10. A pharmaceutical preparation according to claim 7 wherein the pressure is the pressure reading of at least 50 on a Manesty tablet punching machine, model F3.

11. A pharmaceutical preparation according to any one of the preceding claims wherein the size of the micro-capsules is greater than 12 microns.

12. A pharmaceutical preparation according to claim 11 wherein the size of the microcapsules is between 30 microns and 100 microns.

13. A pharmaceutical preparation according to any of the preceding claims wherein the active agent is a naltrexone.

14. A pharmaceutical preparation according to any one of the preceding claims wherein the pharmaceutical preparation is designed for subcutaneous administration.

15. A pharmaceutical preparation according to claim 14 wherein the pharmaceutical preparation is administered in the subcutaneous tissue of the abdominal wall.

16. A pharmaceutical preparation according to any one of the preceding claims wherein the release rate is about 0.1 mg per day to 30 mg per day.

17. A pharmaceutical preparation according to claim 16 wherein the release rate is 0.5 mg per day to 30 mg per day.

18. A pharmaceutical preparation according to claim 16 wherein the release rate is 3.6mg per day to 14.4mg per day.

19. A pharmaceutical preparation according to any of the preceding claims wherein the effective amount of active agent administered is 2.0 to 10g.

20. A pharmaceutical preparation according to any one of the preceding claims wherein the effective amount of active agent is 3.6g to 7.2g.

21. A pharmaceutical preparation according to any one of the preceding claims wherein the percentage of active agent released is 0.1% to 10% per day.

22. A pharmaceutical preparation according to claim 21 wherein the percentage of active agent released is 0.2% to 0.8% per day.

23. A pharmaceutical preparation according to claim 21 wherein the percentage of active agent released is selected from 0.2%, 0.4% or 0.8% per day.

24. A pharmaceutical preparation according to any one of the preceding claims wherein the length of time over which active agent is released more than 40 days.

25. A pharmaceutical preparation according to claim 24 wherein the length of time over which active agent is released more than 45 days.

26. A pharmaceutical preparation according to claim 24 wherein the length of time over which active agent is released for more than 50 days.

27. A pharmaceutical preparation according to claim 24 wherein the length of time over which active agent is released more than three months.

28. A pharmaceutical preparation according to claim 24 wherein the length of time over which active agent is released is more than six months.

29. A pharmaceutical preparation according to claim 24 wherein the length of time over which active agent is released is more than 1 year.

30. A pharmaceutical preparation according to claim 24 wherein the length of time over which active agent is released is more than 18 months.

31. A pharmaceutical preparation according to any one of the preceding claims wherein the biodegradable polymer is long lasting.

32. A pharmaceutical preparation according to claim 31 wherein the length of time that the biodegradable polymer stays in tact is more than 45 days.

33. A pharmaceutical preparation according to claim 31 wherein the length of time that the biodegradable polymer stays in tact is more than 40 days.

34. A pharmaceutical preparation according to claim 31 wherein the length of time that the biodegradable polymer stays in tact is more than 50 days.

35. A pharmaceutical preparation according to claim 31 wherein the length of time that the biodegradable polymer stays in tact is more than three months.

36. A pharmaceutical preparation according to claim 31 wherein the length of time that the biodegradable polymer stays in tact is more than six months.

37. A pharmaceutical preparation according to claim 31 wherein the length of time that the biodegradable polymer stays in tact is more than 1 year.

38. A pharmaceutical preparation according to any one of the preceding claims wherein the biodegradable polymer is selected from any one of polymer(glycolic acid) poly-DL-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycarprolocatone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid caprolactone), polyorthoesters, poly(glycolic acid caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mon-and distearate, and the like.

39. A pharmaceutical preparation according to claim 38 wherein the biodegradable polymer is Purasorb Poly –DL-Lactide.

40. A pharmaceutical preparation according to claim 38 wherein the biodegradable polymer is Poly-DL-lactide/glycolide copolymer.

41. A pharmaceutical preparation according to any one of preceding claims wherein the pharmaceutical preparation comprises one tablet which is coated with at least one layer of biodegradable polymer.

42. A pharmaceutical preparation according to claim 41 wherein the tablet is coated with at least two layers or more of biodegradable polymer.

43. A pharmaceutical preparation according to claim 41 wherein the tablet is coated with at least three layers or more of biodegradable polymer.

44. A pharmaceutical preparation according to any one of the preceding claims wherein the pharmaceutical preparation comprises plurality of tablets coated with at least one coating of biodegradable polymer.

45. A pharmaceutical preparation according to claim 44 wherein there are two coatings of biodegradable polymer.

46. A pharmaceutical preparation according to claim 44 wherein there are three coatings of biodegradable polymer.

47. A pharmaceutical preparation according to any one of the preceding claims wherein the pharmaceutical preparation comprises tablets comprising one or more active agents, each active agent having different rates of release.

48. A pharmaceutical preparation according to any one of the preceding claims wherein the thickness of the coating(s) of one or more biodegradable polymer is 0.001 mm to 1 mm.

49. A pharmaceutical preparation according to claim 48 wherein the thickness of the coating(s) of biodegradable polymer is 0.01 mm to 1 mm.

50. A pharmaceutical preparation according to claim 49 wherein the thickness of the coating(s) of biodegradable polymer is 0.1 mm to 1 mm.

51. A pharmaceutical preparation according to claim 50 wherein the thickness of the coating of biodegradable polymer is 0.6 mm.

52. A pharmaceutical preparation according to any one of the preceding claims

wherein the pharmaceutical preparation comprises a pharmaceutical excipient.

53. A method of treating a patient by administering a pharmaceutical preparation according to any one of claims 1 to 52.

54. A method according to claim 53 wherein the pharmaceutical preparation is administered subcutaneously.

55. A method according to claim 53 or 54 comprising the steps of:

(1) administering implant(s) of the present invention comprising about 3.6g naltrexone where 0.4% per day of naltrexone mass is released;

(2) after about 3 to 6 months repeat step (1); and

(3) after about a further 6 months administering implant(s) of the present invention comprising about 3.6g to 7.2g naltrexone where 0.2% per day of naltrexone mass is released.

56. A method according to claim 53 or 54 comprising the steps of:

(1) administering implant(s) of the present invention comprising about 1.8g releasing at 0.2% per day and a second 1.8g of naltrexone releasing at 0.4% per day;

(2) after about 90 days administering implant(s) of the present invention comprising about 3.6g naltrexone releasing at 0.2% per day; and

(3) if necessary, repeating step (2) after a period of 6 to 18 months.

57. A method of treating a patient according to claim 53 or 54 comprising the steps of:

(1) administering an implant of the present invention comprising about 1.8g to 3.6g where the percentage delivered per day is 0.4% and 0.2% respectively.

(2) after about 12 months administering an implant(s) of the present invention comprising 5.4g naltrexone where 0.2% per day of naltrexone mass is released.

58. A method for inserting one or more implant(s) into a tissue of a mammal comprising the following steps:

a) making a small incision into the tissue with a needle and first sheath;

b) withdrawing the needle from the first sheath but leaving the first sheath in the tissue;

c) dilating the opening of the incision by inserting a dilator and second sheath of larger diameter through the boy of the first sheath;

d) withdrawing the dilator from the second sheath, but leaving second sheath in the tissue; and

e) disbursing the implant(s) from a sheath filled with implant(s) by inserting said sheath into the final sheath inserted into the tissue and pushing a dilator into the sheath thereby releasing said implant(into the tissue).

59. A method according to claim 58 wherein the diameter of the needle required for the initial incision is less than 3 mm.

60. A method according to claim 58 wherein the diameter of the needle required for the initial incision is less than 2 mm.

61. A method according to any of the preceding claims wherein the method is administered on a mammal.

62. A method according to claim 61 wherein the method is administered on a human.

63. A method according claim 62 wherein the method is administered on subcutaneous tissue of a human.

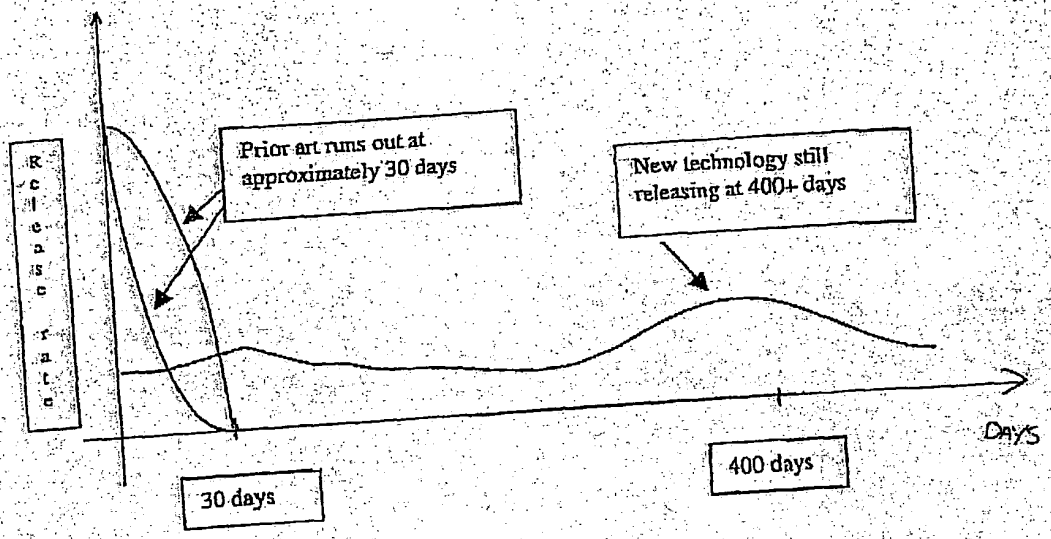

Release rate
Prior art runs out at approximately 30 days
New technology still releasing at 400+ days
Days
30 days
400 days

Figure 1

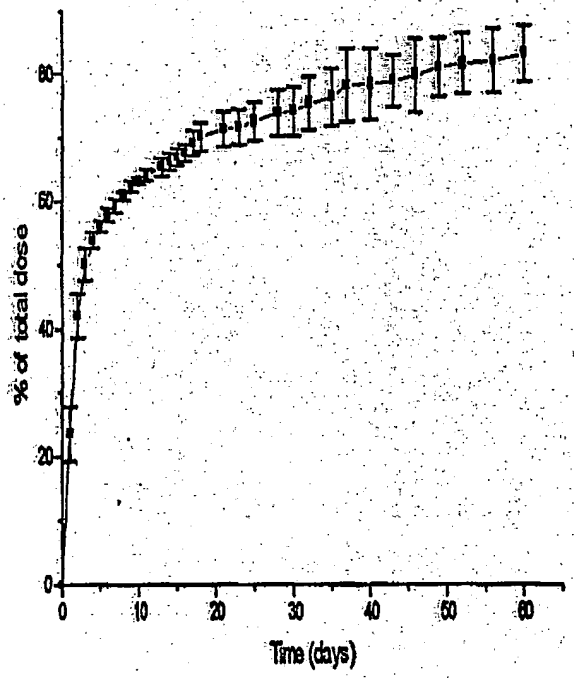


Figure 2

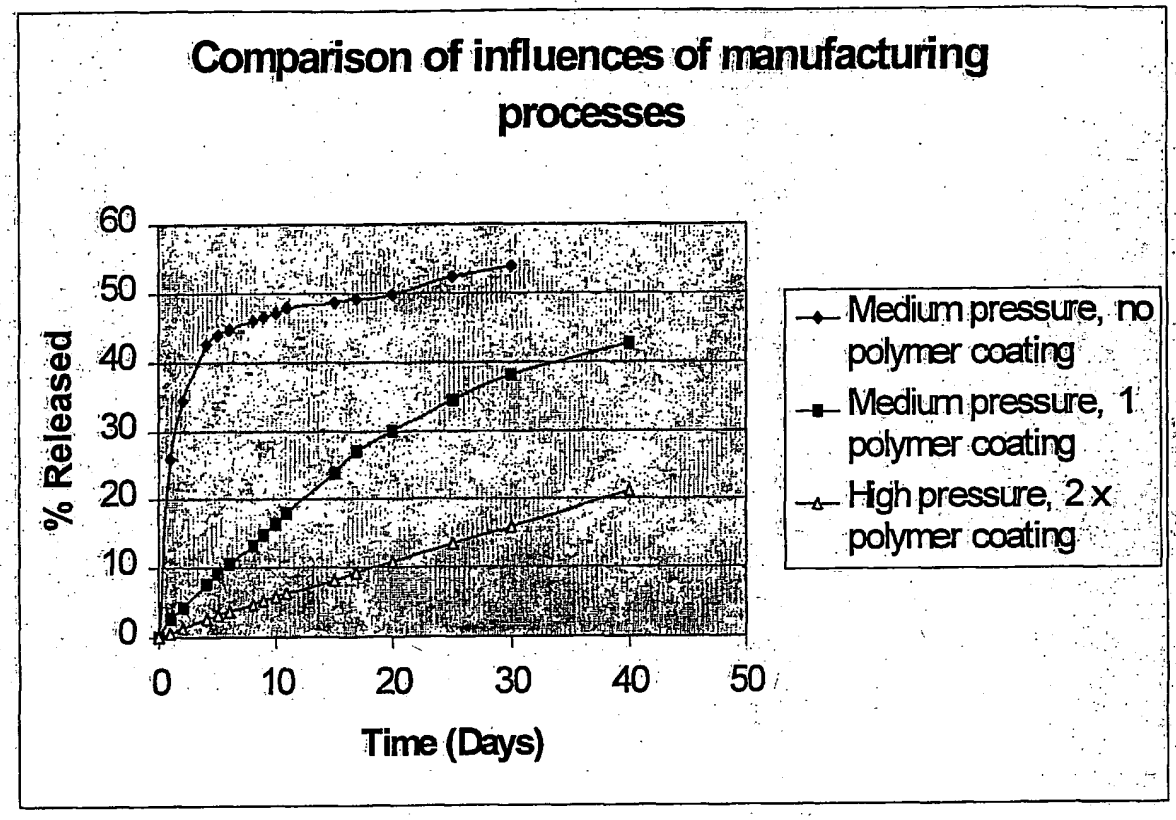

Comparison of influences of manufacturing processes
% Released
60
50
40
30
20
10
0
0
10
20
30
40
50
Time (Days)
Medium pressure, no polymer coating
Medium pressure, 1 polymer coating
High pressure, 2 x polymer coating

Figure 3

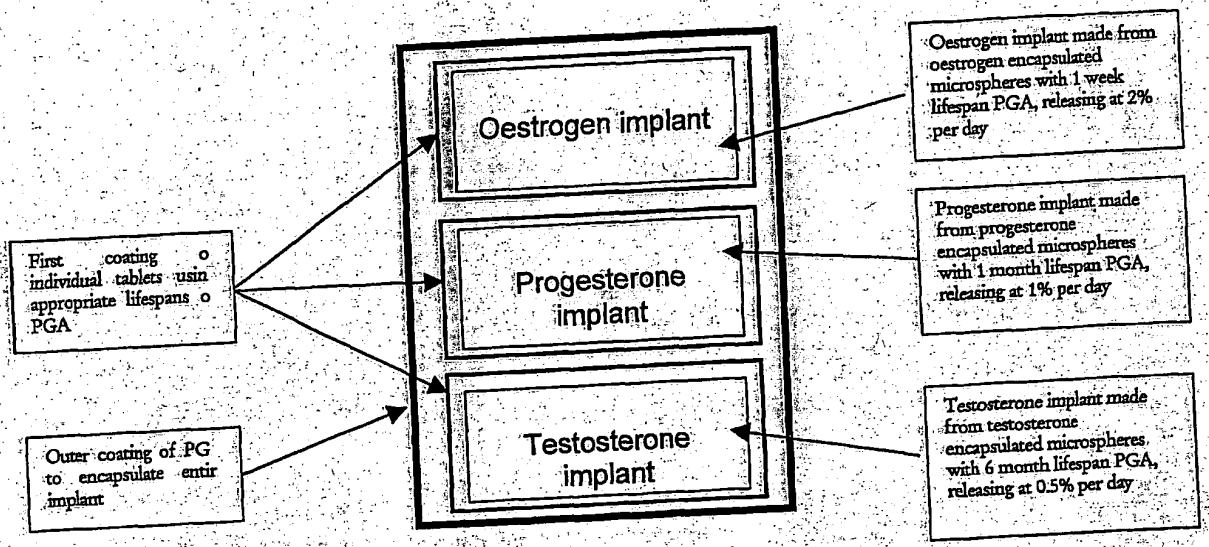

Oestrogen implant
Progesterone implant
Testosterone implant
First coating o individual tablets usin appropriate lifespans o PGA
Outer coating of PG to encapsulate entir implant
Oestrogen implant made from oestrogen encapsulated microspheres with 1 week lifespan PGA, releasing at 2% per day
Progesterone implant made from progesterone encapsulated microspheres with 1 month lifespan PGA, releasing at 1% per day
Testosterone implant made from testosterone encapsulated microspheres with 6 month lifespan PGA, releasing at 0.5% per day

Figure 4

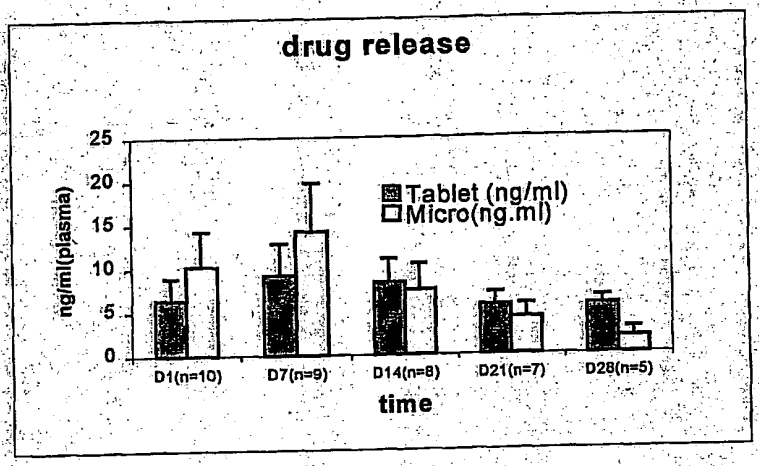


Figure 5 Naltrexone levels in the blood plasma of rats are shown above

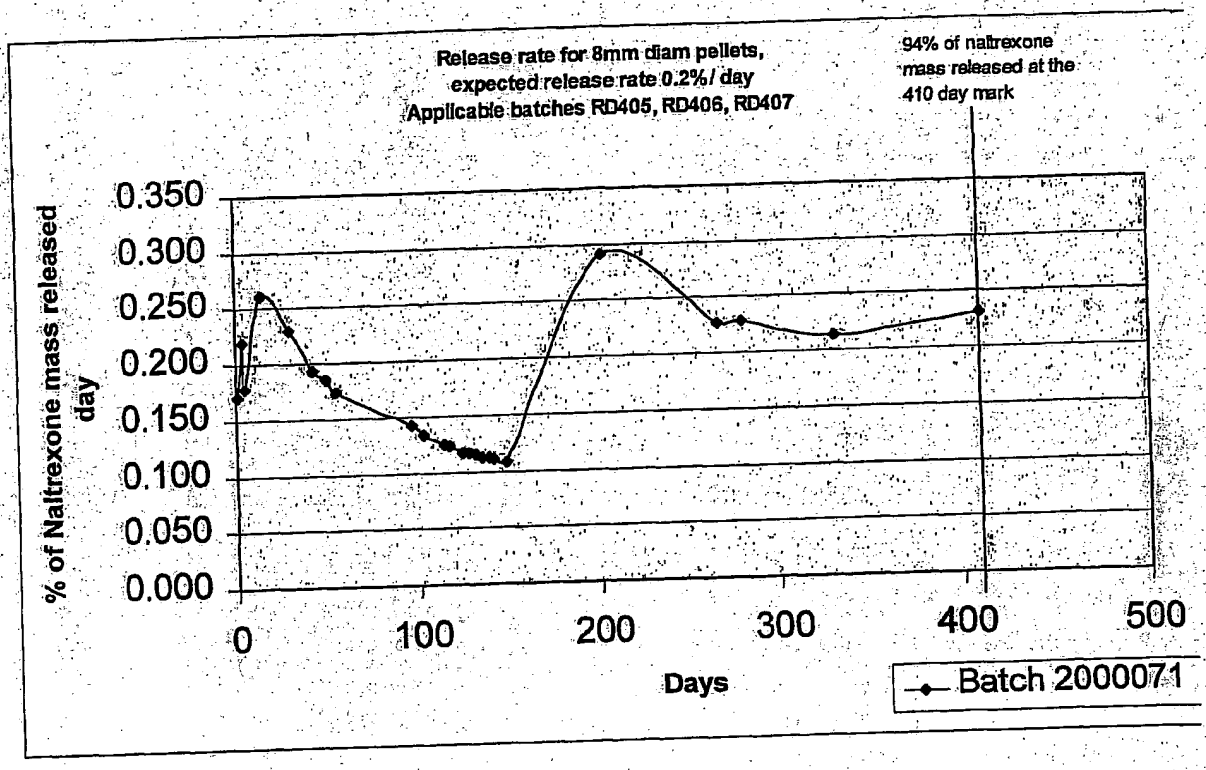

Release rate for 8mm diam pellets,
expected release rate 0.2%/ day
Applicable batches RD405, RD406, RD407
94% of naltrexone
mass released at the
410 day mark
% of Naltrexone mass released
day
0.350
0.300
0.250
0.200
0.150
0.100
0.050
0.000
0
100
200
300
400
500
Days
Batch 2000071

Figure 6

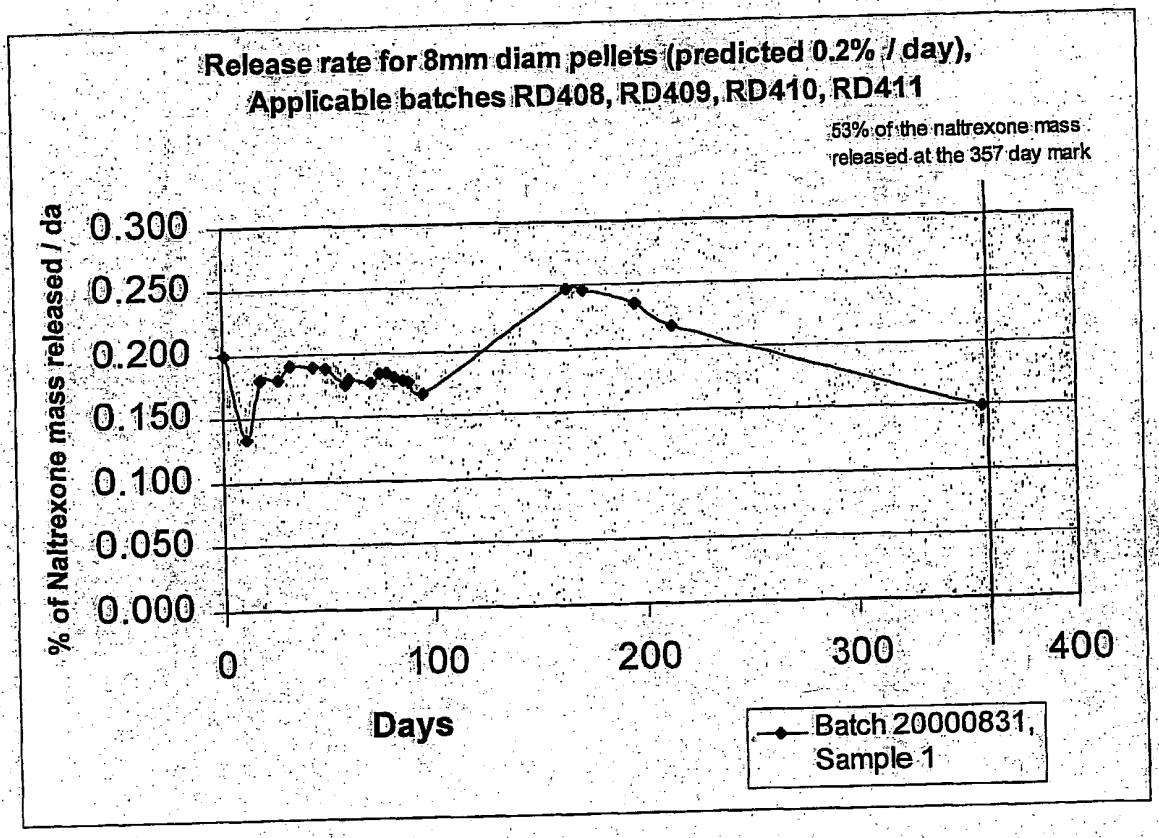

Release rate for 8mm diam pellets (predicted 0.2% / day),
Applicable batches RD408, RD409, RD410, RD411
53% of the naltrexone mass released at the 357 day mark
% of Naltrexone mass released / da
0.300
0.250
0.200
0.150
0.100
0.050
0.000
0
100
200
300
400
Days
Batch 20000831, Sample 1

Figure 7

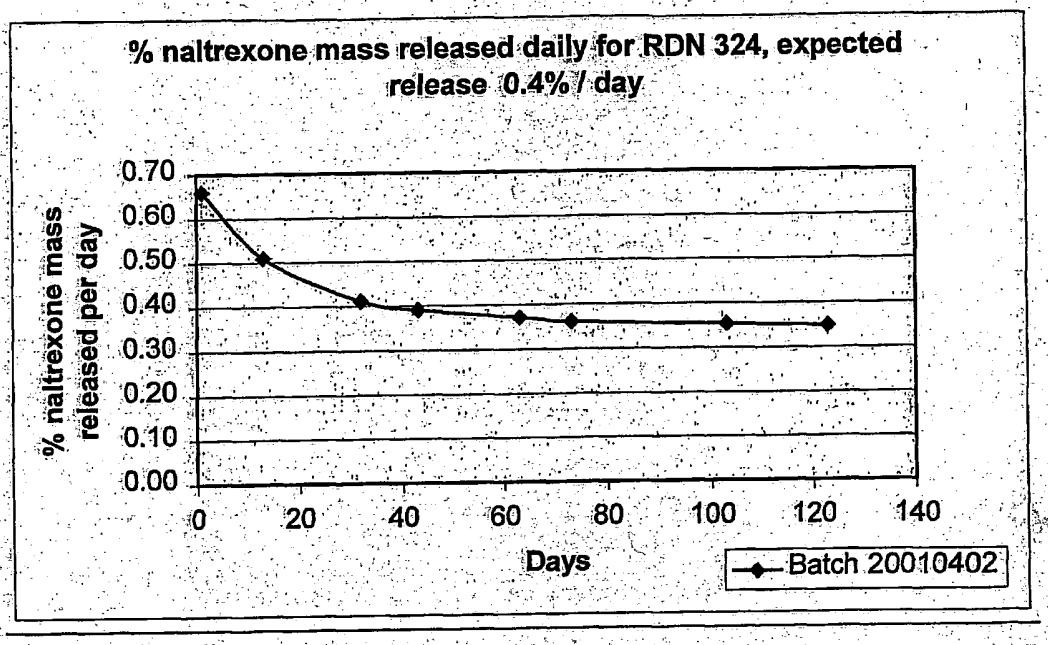

% naltrexone mass released daily for RDN 324, expected release 0.4% / day
% naltrexone mass released per day
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
20
40
60
80
100
120
140
Days
Batch 20010402

Figure 8

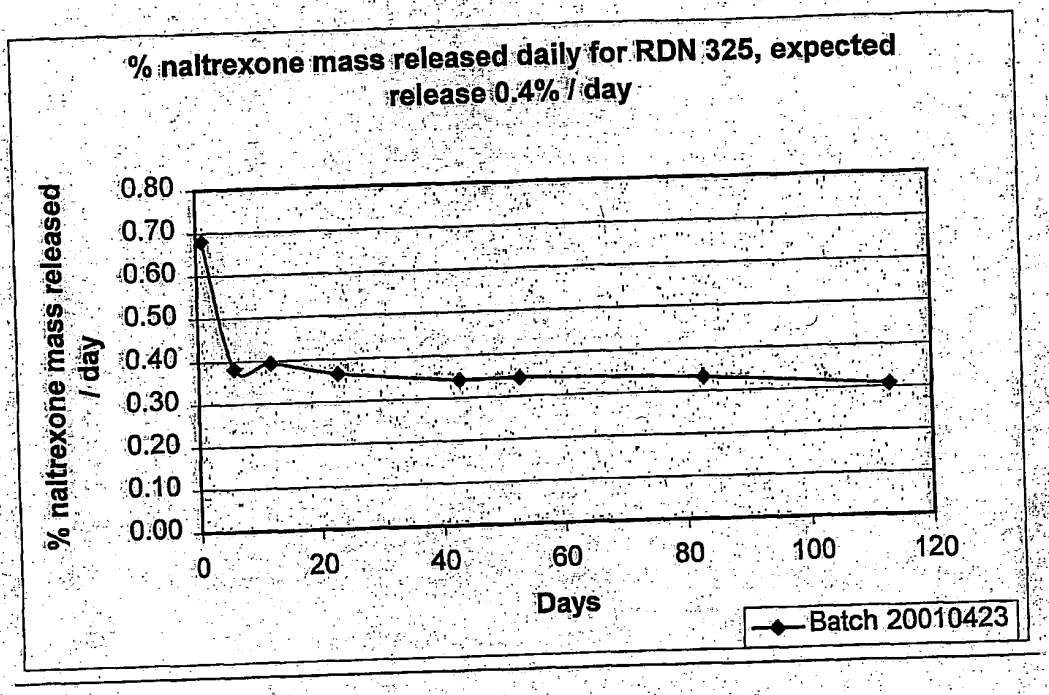

% naltrexone mass released daily for RDN 325, expected release 0.4% / day
% naltrexone mass released / day
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
20
40
60
80
100
120
Days
Batch 20010423

Figure 9

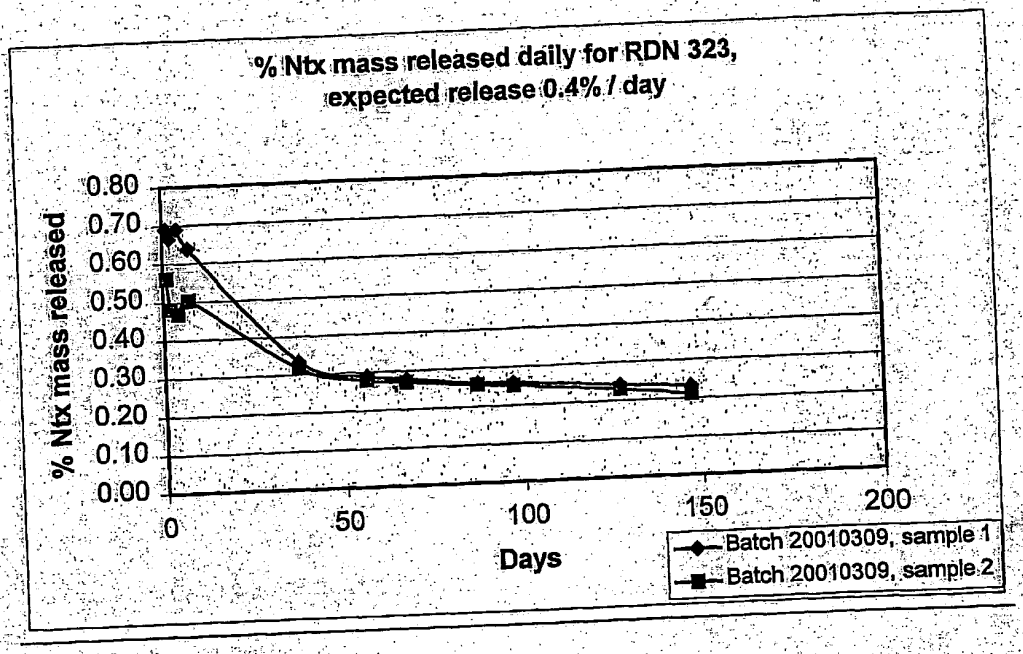

% Ntx mass released daily for RDN 323,
expected release 0.4% / day
% Ntx mass released
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
50
100
150
200
Days
Batch 20010309, sample 1
Batch 20010309, sample 2

Figure 10

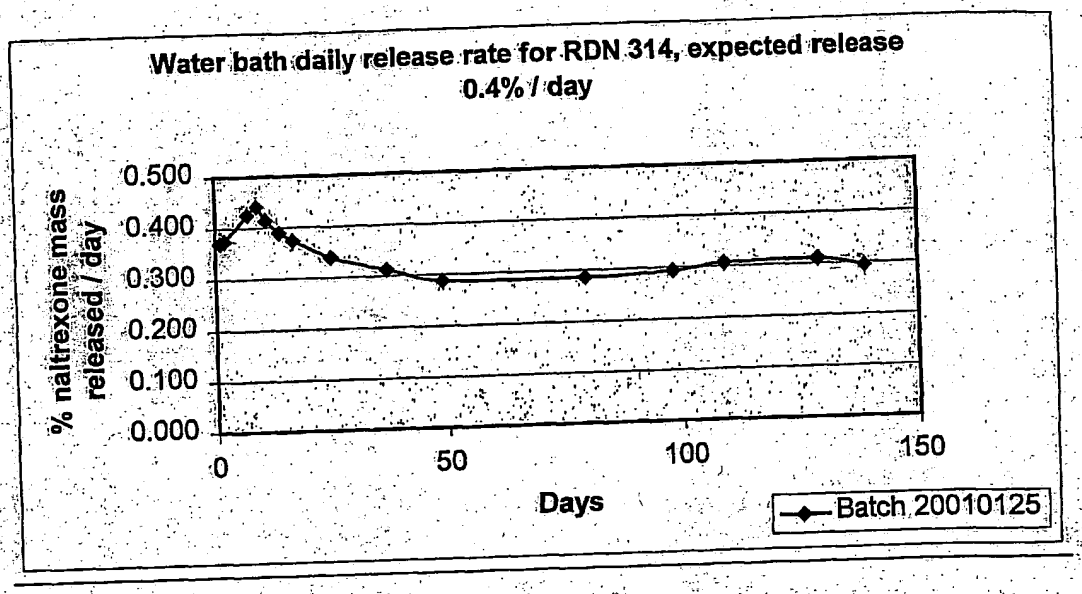

Water bath daily release rate for RDN 314, expected release 0.4% / day
% naltrexone mass released / day
0.500
0.400
0.300
0.200
0.100
0.000
0
50
100
150
Days
Batch 20010125

Figure 11

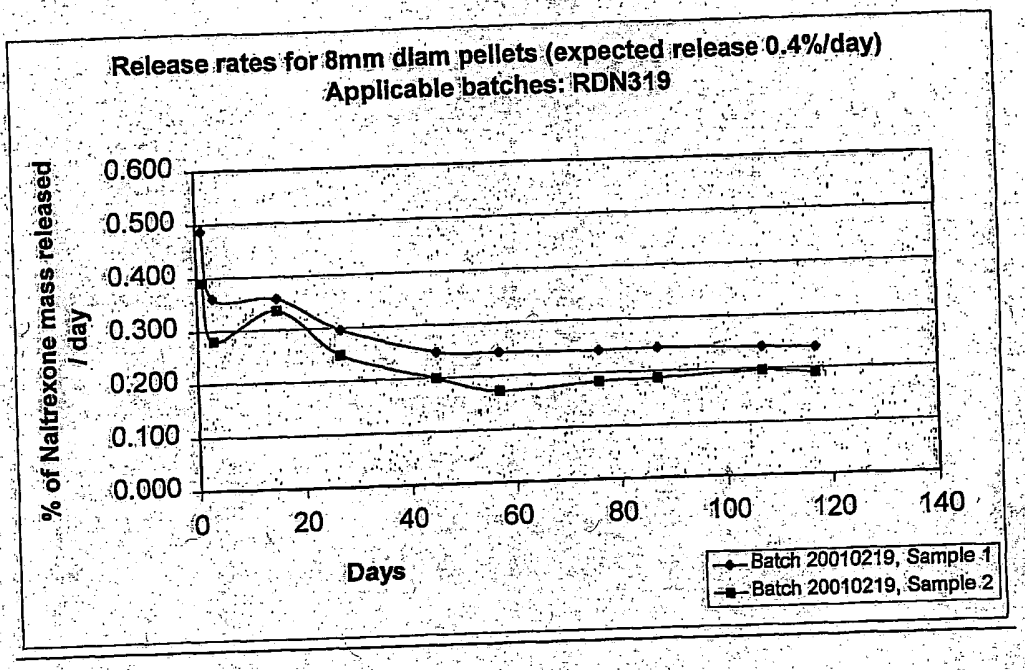

Release rates for 8mm diam pellets (expected release 0.4%/day)
Applicable batches: RDN319
% of Naltrexone mass released / day
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
20
40
60
80
100
120
140
Days
Batch 20010219, Sample 1
Batch 20010219, Sample 2

Figure 12

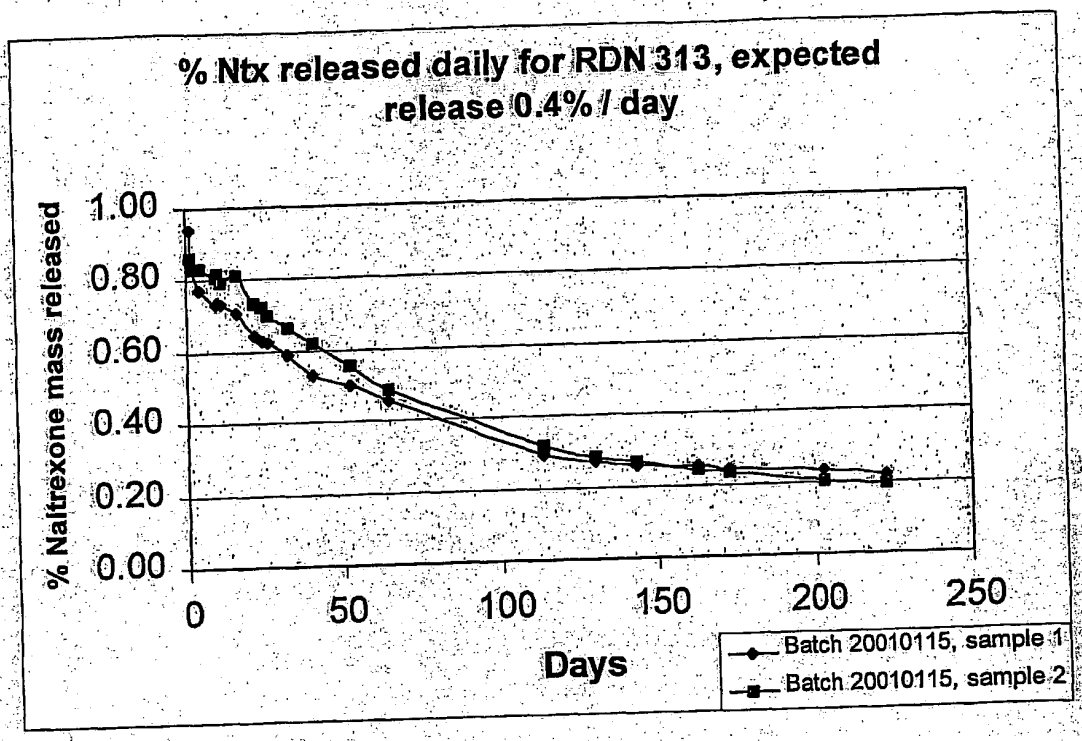

% Ntx released daily for RDN 313, expected release 0.4% / day
% Naltrexone mass released
1.00
0.80
0.60
0.40
0.20
0.00
0
50
100
150
200
250
Days
Batch 20010115, sample 1
Batch 20010115, sample 2

Figure 13

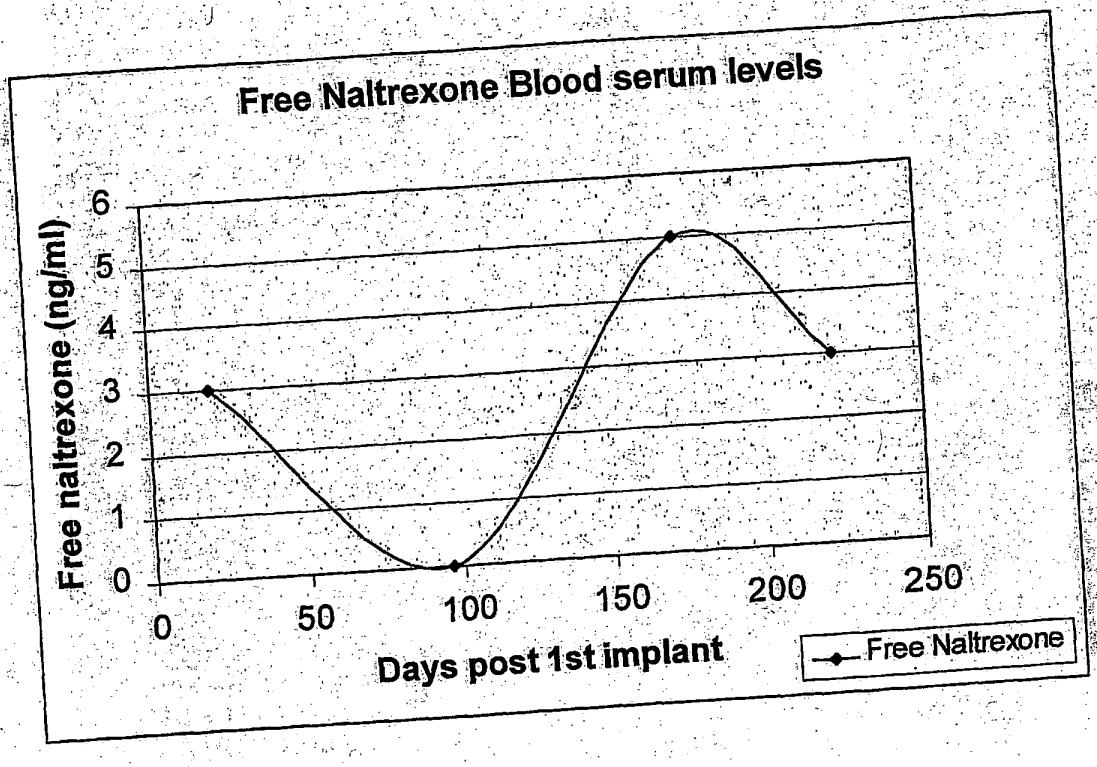

Free Naltrexone Blood serum levels
Free naltrexone (ng/ml)
0
1
2
3
4
5
6
0
50
100
150
200
250
Days post 1st implant
Free Naltrexone

Figure 14

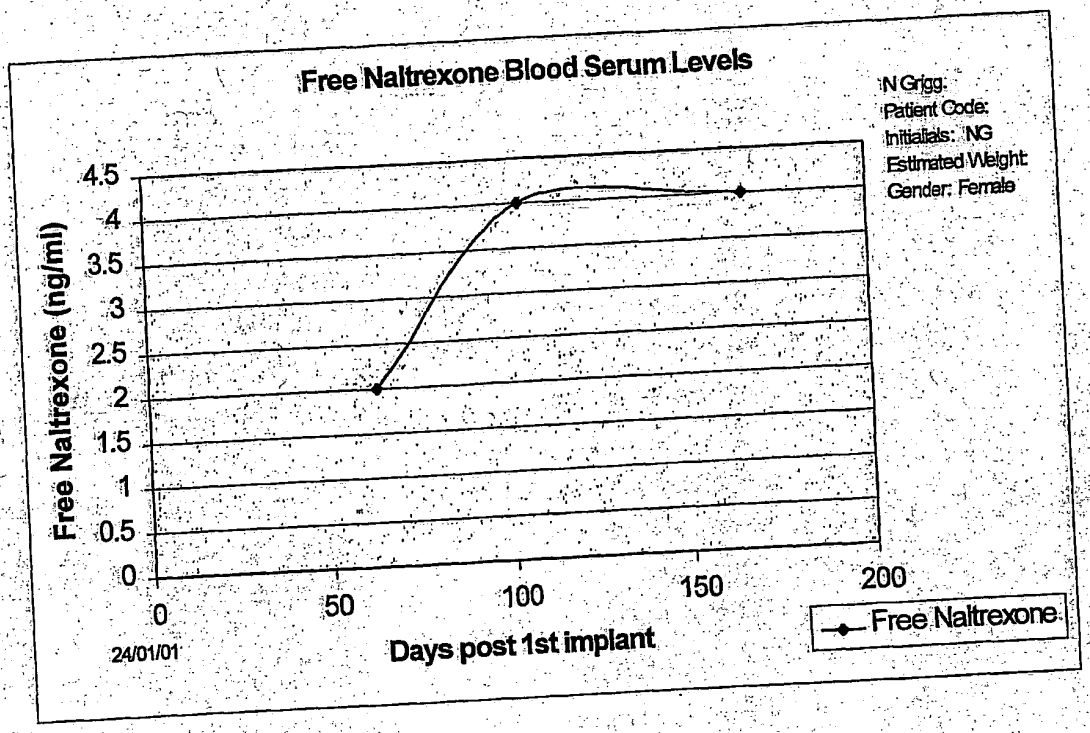

Free Naltrexone Blood Serum Levels
N Grigg:
Patient Code:
Initialtals: NG
Estimated Weight:
Gender: Female
Free Naltrexone (ng/ml)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
50
100
150
200
24/01/01
Days post 1st implant
Free Naltrexone

Figure 15

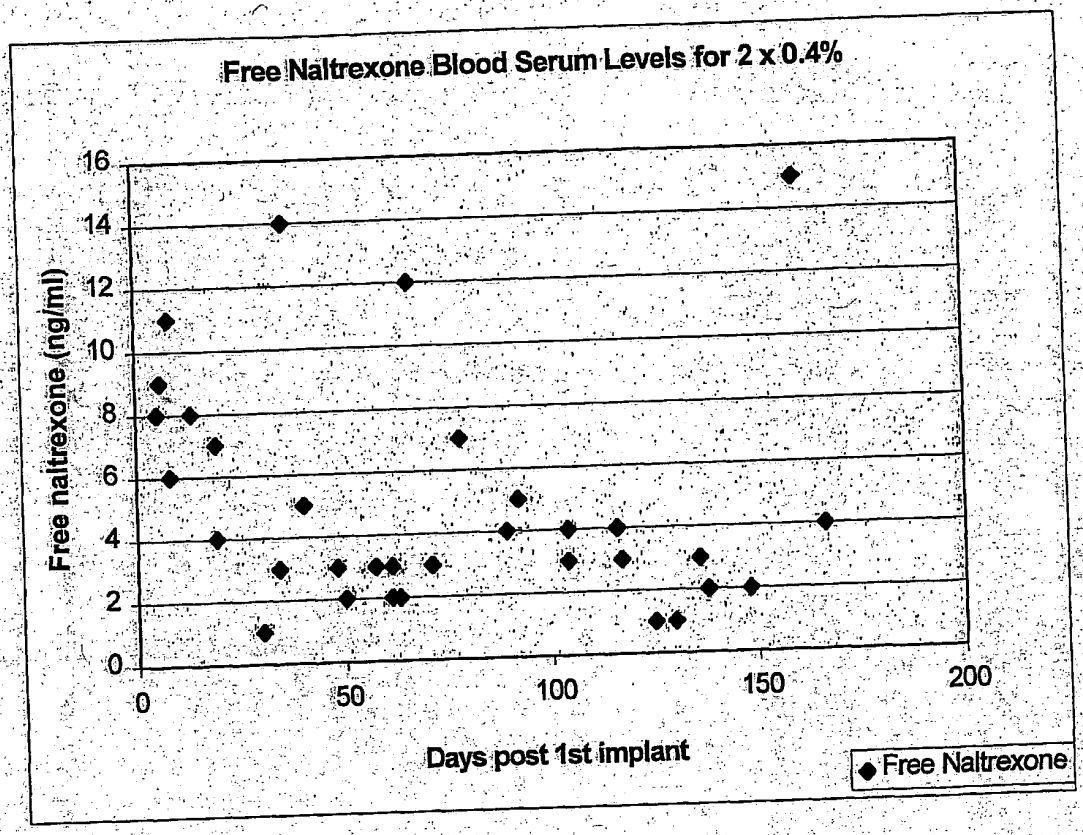

Free Naltrexone Blood Serum Levels for 2 x 0.4%
Free naltrexone (ng/ml)
16
14
12
10
8
6
4
2
0
0
50
100
150
200
Days post 1st implant
Free Naltrexone

Figure 16

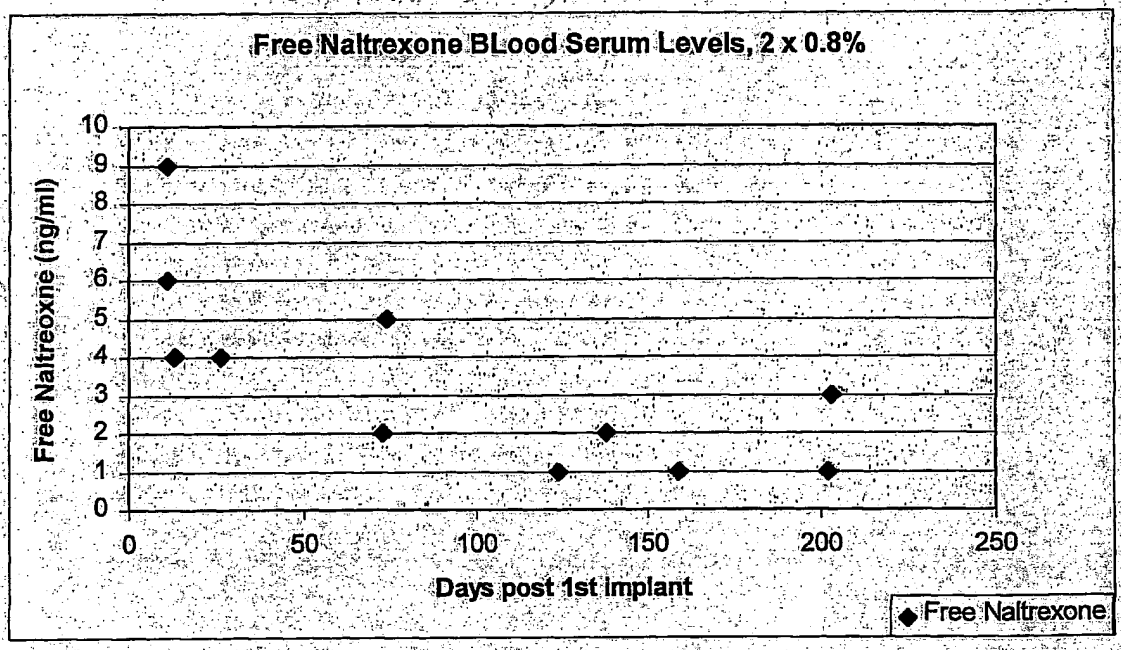

Free Naltrexone BLood Serum Levels, 2 x 0.8%
Free Naltreoxne (ng/ml)
10
9
8
7
6
5
4
3
2
1
0
0
50
100
150
200
250
Days post 1st Implant
Free Naltrexone

Figure 17

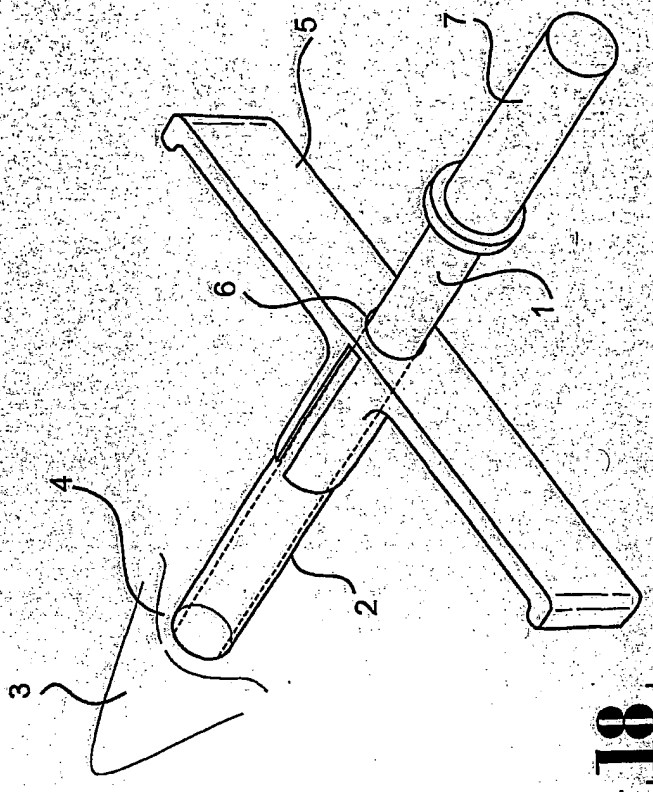


Fig 18

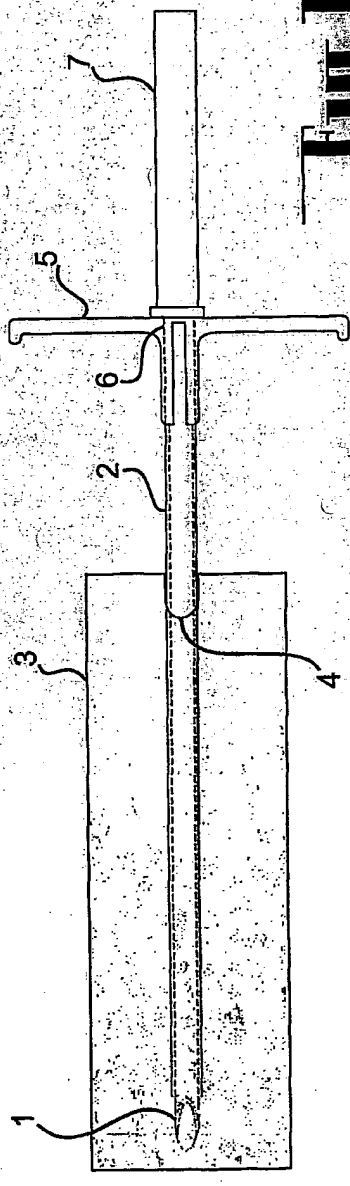


Fig 18a

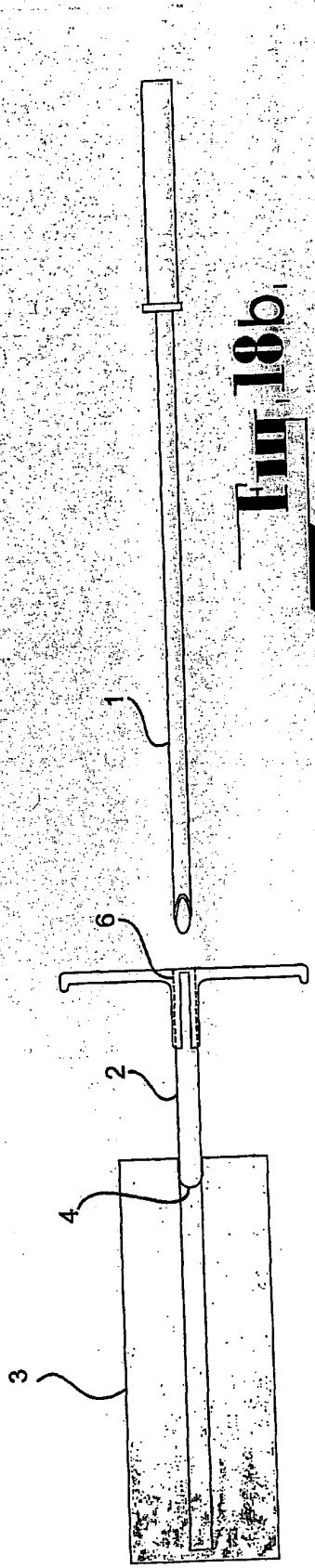


Fig. 18b

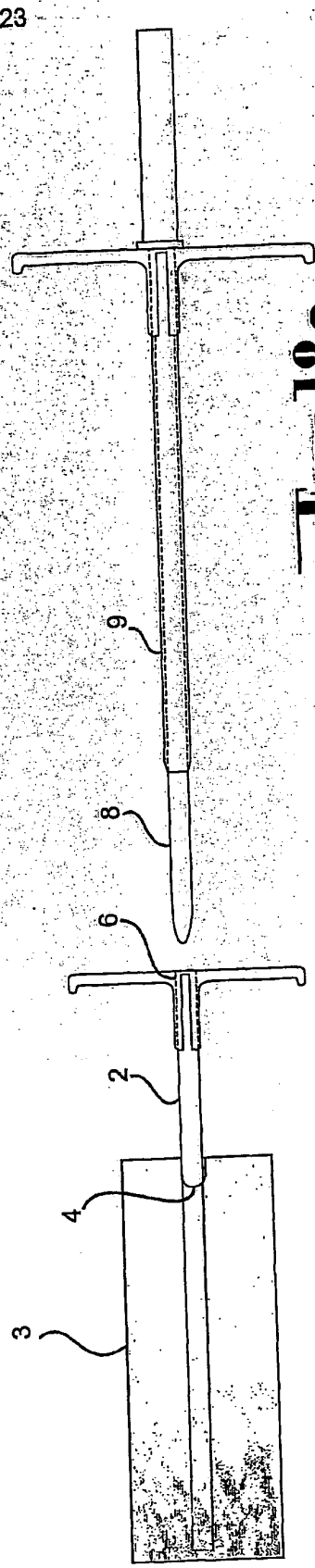


Fig. 18c

Fig 8d

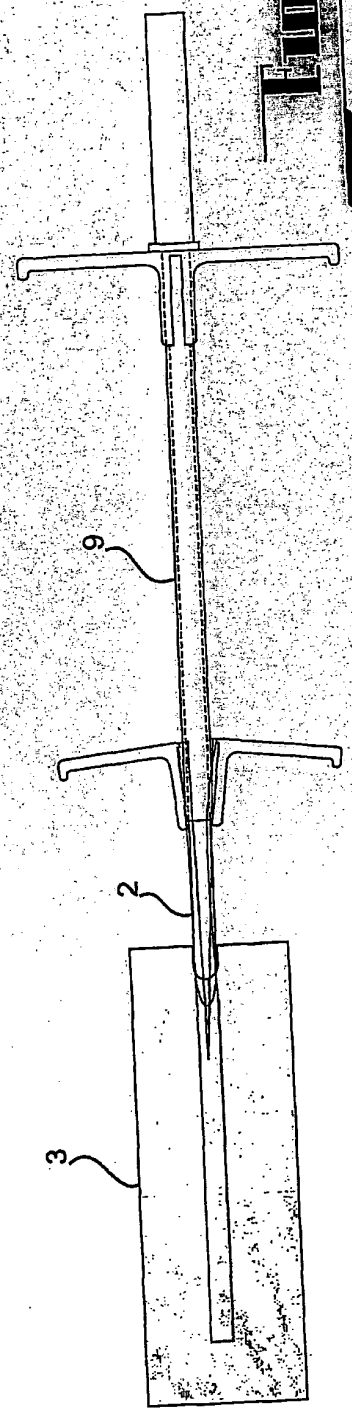
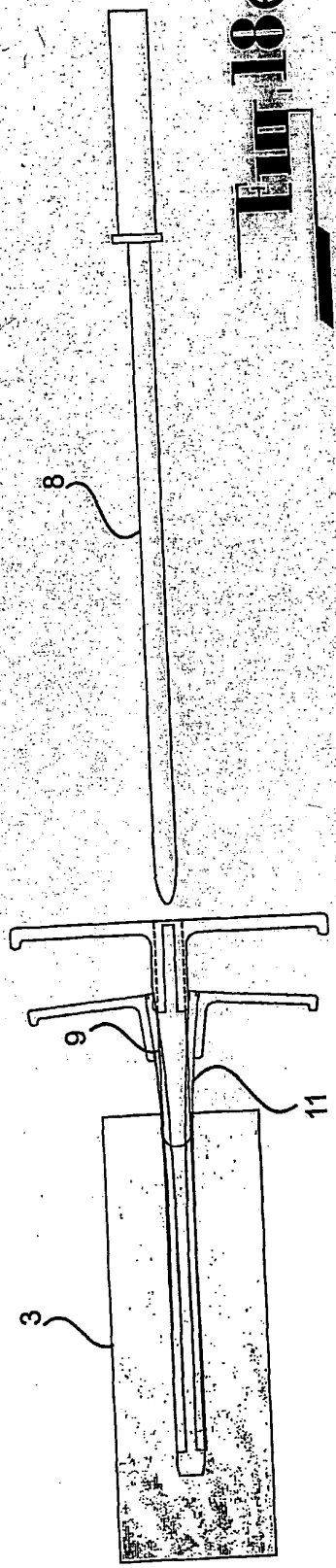


Fig 8e



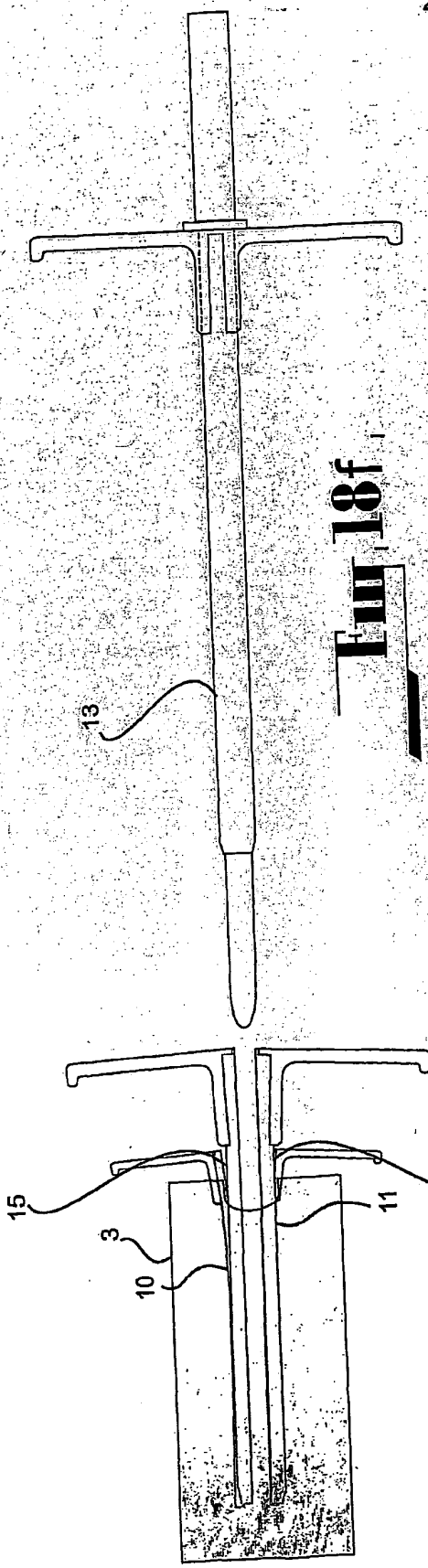


Fig 18f

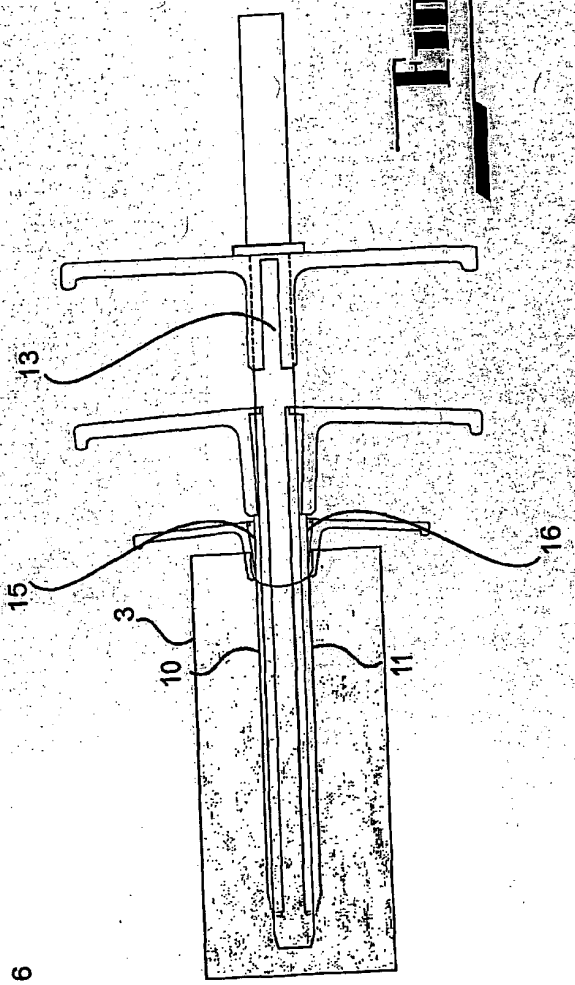


Fig 18g

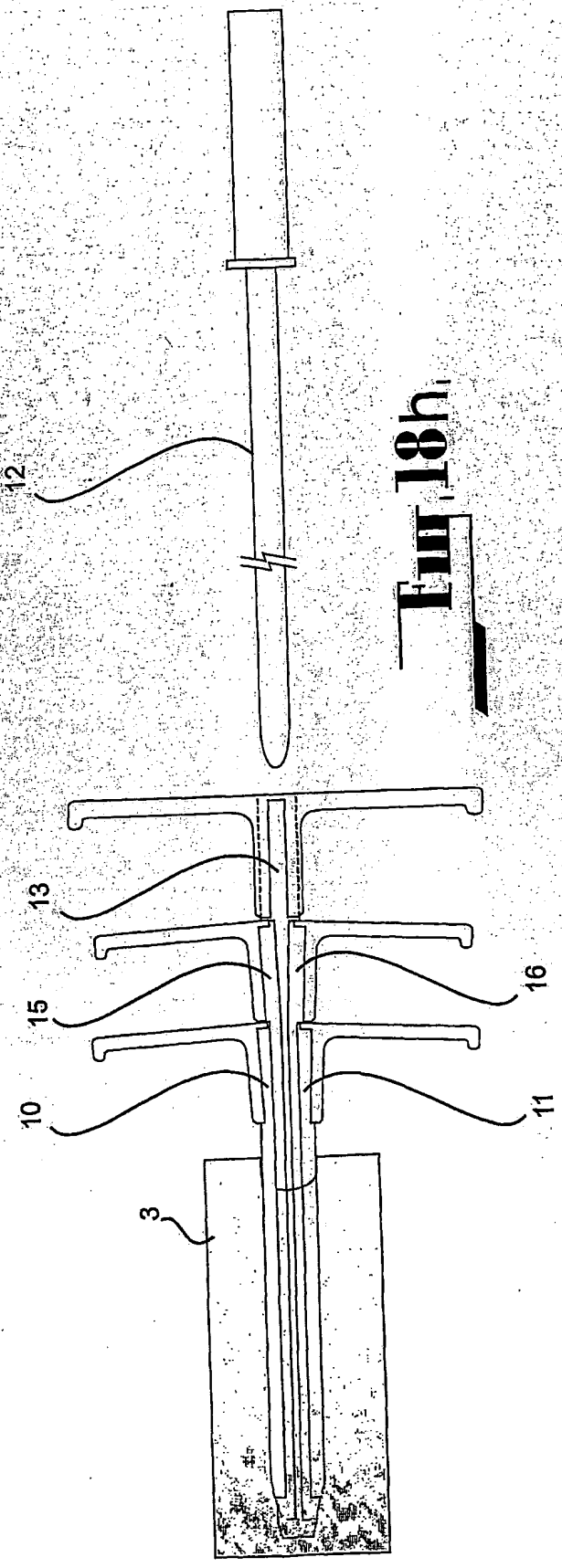


Fig 18h

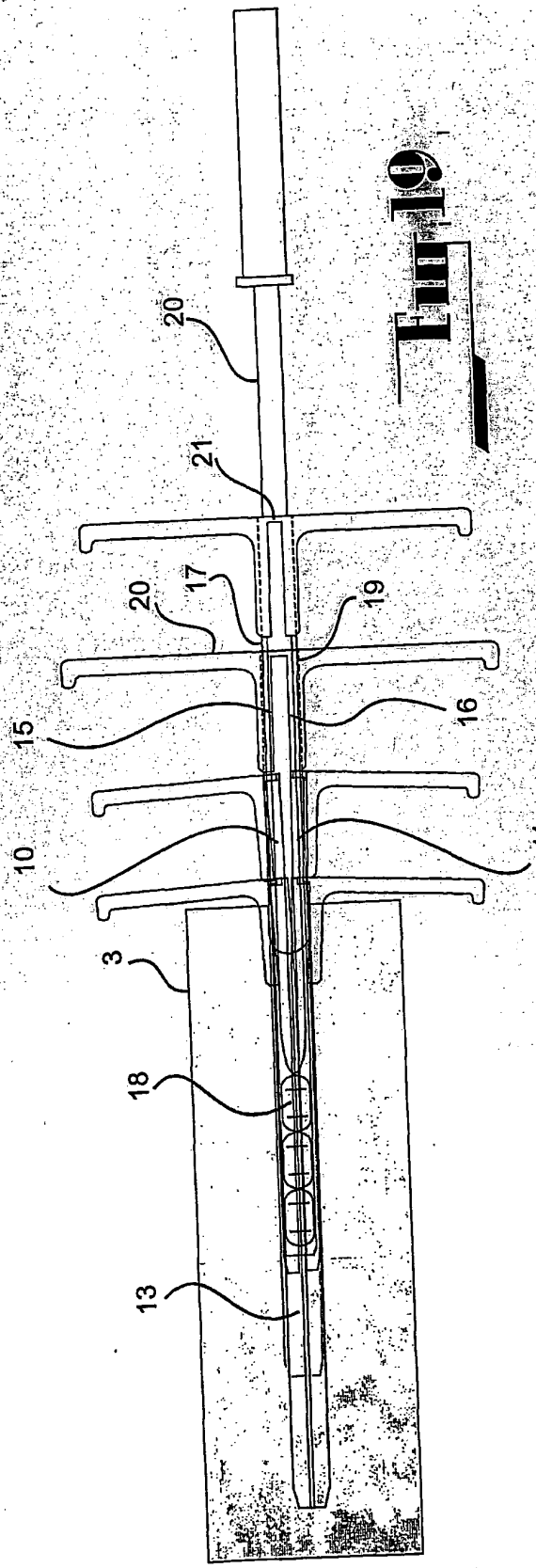


Fig 19

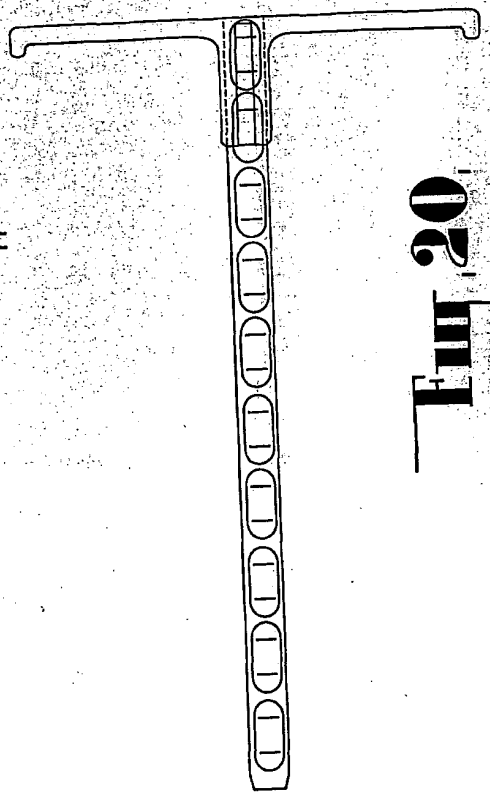


Fig 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01107

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.[7]: A61K 009/00, A61K 009/26, A61K 009/30, A61K 031/485; A61P 25/36. A61M 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, SEARCH TERMS AS BELOW. Refer to electronic database consulted below

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AU: IPC AS ABOVE. A61M 31/00, 37/00

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPAT, CAPLUS: microcapsule, tablet, implant, controlled, sustained, slow, release, coat, tablet.
DWPI keywords: insert introduce implant place inject capsule microcapsule tablet pill seed insert dilate enlarge widen expand and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/27843A (Advanced Polymer Systems, Inc.) 7 August 1997 See whole document	1 to 12, 16 to 23, 38, 41, 47 to 53
X	GB 1 598 458A (Hoechst UK Limited) 23 September 1981 See whole document (especially Claims 1, 20 and 21)	1 to 12, 16 to 23, 38, 41, 47 to 53
A	Harrigan, S.E. et al. "Pharmacological Evaluation of Narcotic Antagonist Delivery Systems in Rhesus Monkeys" NIDA Research Monograph Vol. 28 1981, pages 77 -92 See whole document	1 to 57

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2001	16 NOV 2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer MICHAEL GRIEVE Telephone No : (02) 6283 2267

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01107

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Reuning, R.H. et al. "Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems" NIDA Research Monograph Vol. 28 1981, pages 172 - 184 See whole document	1 to 57
X	WO 00/02616A1 (Innerdyne Inc.) 20 January 2000 Page 2 line 30 to page 4 line 27	58 to 63
A	US 5304119A (Balaban et al.) 19 April 1994	58 to 63
A	US 5183464A (Dubrul et al.) 2 February 1993	58 to 63

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01107

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims 1 to 57 are directed to pharmaceutical preparations for the sustained release of an active agent, comprising an outer portion prepared from one or more layers of a biodegradable polymer, and an inner portion comprising a plurality of active agent-containing microcapsules compressed into the form of a tablet.

2. Claims 58 to 63 are directed to a method for inserting one or more implants into the tissue of a mammal.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:**1 to 57**

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01107

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member					
WO 97/27843	AU	17519/97				
GB 1598458	AU	34651/78	BE	865633	CA	1110972
	CH	640727	DE	2813146	DK	1430/78
	FR	2385388	IT	1095559	JP	53142520
	NL	7803496	SE	7803661		
WO 00/02616	EP	1094862	US	6245052		
US 5304119						
US 5183464	AU	16347/92	CA	2109416	DE	69220792
	EP	585406	WO	92/20399		

END OF ANNEX